TITLE OF THE INVENTION

KINASE INHIBITORS

BACKGROUND OF THE INVENTION

The present invention relates to compounds which inhibit, regulate and/or modulate kinase signal transduction, compositions which contain these compounds, and methods of using them to treat kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, retinal ischemia, macular edema, inflammatory diseases, and the like in mammals.

Kinases can be split into two main groups, tyrosine kinases such as KDR or Flk-1 and serine/threonine kinases such as cyclin dependent kinases or Cdk.

Tyrosine kinases are a class of enzymes that catalyze the transfer of the terminal phosphate of adenosine triphosphate to tyrosine residues in protein substrates. Tyrosine kinases are believed, by way of substrate phosphorylation, to play critical roles in signal transduction for a number of cell functions. Though the exact mechanism of signal transduction is still unclear, tyrosine kinases have been shown to be important contributing factors in cell proliferation, carcinogenesis, cell differentiation and apoptosis.

Tyrosine kinases can be categorized as receptor type or non-receptor type. Receptor type tyrosine kinases have an extracellular, a transmembrane, and an intracellular portion, while non-receptor type tyrosine kinases are wholly intracellular.

The receptor type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. In fact, about twenty different subfamilies of receptor type tyrosine kinases have been identified. One tyrosine kinase subfamily, designated the HER subfamily, is comprised of EGFR, HER2, HER3, and HER4. Ligands of this subfamily of receptors include epithileal growth factor, TGF-α, amphiregulin, HB-EGF, betacellulin and heregulin. Another subfamily of these receptor type tyrosine kinases is the insulin subfamily, which includes INS-R, IGF-IR, and IR-R. The PDGF subfamily includes the PDGF-α and -β receptors, CSFIR, c-kit and FLK-II. Then there is the FLK family which is comprised of the kinase insert domain receptor (KDR), fetal liver kinase-1 (FLK-1), fetal liver kinase-4 (FLK-4) and the fms-like tyrosine kinase-1 (flt-1). The PDGF and FLK families are usually considered together due to the similarities of the two groups. For a detailed discussion of the receptor type tyrosine kinases, see Plowman et al., *DN&P* 7(6):334-339 (1994), which is hereby incorporated by reference.

The non-receptor type of tyrosine kinases is also comprised of numerous subfamilies, including Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack, and LIMK. Each

of these subfamilies is further sub-divided into varying receptors. For example, the Src subfamily is one of the largest and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, and Yrk. The Src subfamily of enzymes has been linked to oncogenesis. For a more detailed discussion of the non-receptor type of tyrosine kinases, see Bolen, *Oncogene* 8:2025-2031 (1993), which is hereby incorporated by reference.

Both receptor type and non-receptor type tyrosine kinases are implicated in cellular signaling pathways leading to numerous pathogenic conditions, including cancer, psoriasis and hyperimmune responses.

Several receptor type tyrosine kinases, and the growth factors that bind thereto, have been suggested to play a role in angiogenesis, although some may promote angiogenesis indirectly Mustonen and Alitalo, *J. Cell Biol.* 129:895-898 (1995). One such receptor type tyrosine kinase is fetal liver kinase 1 or FLK-1. The human analog of FLK-1 is the kinase insert domain-containing receptor KDR, which is also known as vascular endothelial cell growth factor receptor 2 or VEGFR-2, since it binds VEGF with high affinity. Finally, the murine version of this receptor has also been called NYK. Oelrichs et al., *Oncogene* 8(1):11-15 (1993). VEGF and KDR are a ligand-receptor pair that play an important role in the proliferation of vascular endothelial cells, and the formation and sprouting of blood vessels, termed vasculogenesis and angiogenesis, respectively.

Angiogenesis is characterized by excessive activity of vascular endothelial growth factor (VEGF). VEGF is actually comprised of a family of ligands. Klagsburn and D'Amore, *Cytokine &Growth Factor Reviews* 7:259-270 (1996). VEGF binds the high affinity membrane-spanning tyrosine kinase receptor KDR and the related fms-like tyrosine kinase-1, also known as Flt-1 or vascular endothelial cell growth factor receptor 1 (VEGFR-1). Cell culture and gene knockout experiments indicate that each receptor contributes to different aspects of angiogenesis. KDR mediates the mitogenic function of VEGF whereas Flt-1 appears to modulate non-mitogenic functions such as those associated with cellular adhesion. Inhibiting KDR thus modulates the level of mitogenic VEGF activity. In fact, tumor growth has been shown to be susceptible to the antiangiogenic effects of VEGF receptor antagonists. Kim et al., *Nature* 362:841-844 (1993).

Solid tumors can therefore be treated by tyrosine kinase inhibitors since these tumors depend on angiogenesis for the formation of the blood vessels necessary to support their growth. These solid tumors include histiocytic lymphoma, cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung, including lung adenocarcinoma and small cell lung cancer. Additional examples include cancers in which overexpression or activation of Raf-activating oncogenes (e.g., *K-ras, erb-B*) is observed. Such cancers include pancreatic and breast

carcinoma. Accordingly, inhibitors of these tyrosine kinases are useful for the prevention and treatment of proliferative diseases dependent on these enzymes.

The angiogenic activity of VEGF is not limited to tumors. VEGF accounts for most of the angiogenic activity produced in or near the retina in diabetic retinopathy. This vascular growth in the retina leads to visual degeneration culminating in blindness. Ocular VEGF mRNA and protein are elevated by conditions such as retinal vein occlusion in primates and decreased pO_2 levels in mice that lead to neovascularization. Intraocular injections of anti-VEGF monoclonal antibodies or VEGF receptor immunofusions inhibit ocular neovascularization in both primate and rodent models. Regardless of the cause of induction of VEGF in human diabetic retinopathy, inhibition of ocular VEGF is useful in treating the disease.

Expression of VEGF is also significantly increased in hypoxic regions of animal and human tumors adjacent to areas of necrosis. VEGF is also upregulated by the expression of the oncogenes *ras*, *raf*, *src* and mutant *p53* (all of which are relevant to targeting cancer). Monoclonal anti-VEGF antibodies inhibit the growth of human tumors in nude mice. Although these same tumor cells continue to express VEGF in culture, the antibodies do not diminish their mitotic rate. Thus tumor-derived VEGF does not function as an autocrine mitogenic factor. Therefore, VEGF contributes to tumor growth *in vivo* by promoting angiogenesis through its paracrine vascular endothelial cell chemotactic and mitogenic activities. These monoclonal antibodies also inhibit the growth of typically less well-vascularized human colon cancers in athymic mice and decrease the number of tumors arising from inoculated cells.

Viral expression of VEGF-binding constructs of Flk-1 or Flt-1 (the mouse KDR receptor homologue), truncated to eliminate the cytoplasmic tyrosine kinase domains but retain the membrane anchors, virtually abolishes the growth of a transplantable glioblastoma in mice. Tumor growth is abolished presumably by a dominant negative mechanism during VEGF receptor homodimerization. Embryonic stem cells, which normally grow as solid tumors in nude mice, do not produce detectable tumors if both VEGF alleles are knocked out. Taken together, these data indicate the role of VEGF in the growth of solid tumors. Inhibition of KDR or Flt-1 is implicated in pathological angiogenesis, and these receptors are useful in the treatment of diseases in which angiogenesis is part of the overall pathology, e.g., inflammation, diabetic retinal vascularization, as well as various forms of cancer since tumor growth is known to be dependent on angiogenesis. Weidner et al., *N. Engl. J. Med.* 324:1-8 (1991).

The cyclin-dependent protein kinases are regulators of the timing and coordination of eukaryotic cell cycle events. Norbury, C., and Nurse, P. (1992) *Annu. Rev. Biochem.* 61, 441-470, Sher, C.J. (1996) *Science* 274, 1672-1677. As such, cyclin dependent kinases, their regulators and substrates are the targets of genetic alterations in many human

cancers. Kamb, A. et al. (1994) *Science* 264, 436-440, Nobori, et al. (1994) *Nature* 368, 753-756. Spruck, C.H. et al. *Nature* 370, 183-184, Hunter, T. and Pines, J. (1991) *Cell* 66, 1071-1074, Keyomarsi, K. and Pardee, A.B. (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90, 1112-1116 and Wang, T.C. (1994) *Nature* 369, 669-671.

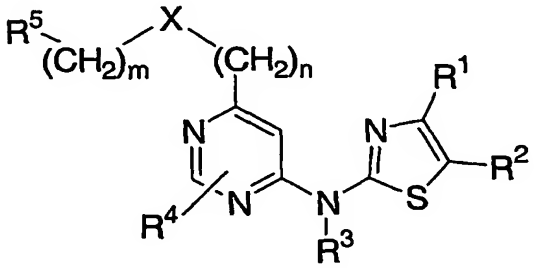
Members of the cyclin dependent kinase family include Cdk2 and Cdk4. Both are active in the G_1 phase of cell cycle and regulate entry into the G_1/S phase transition. In one pathway, these kinases regulate the phosphorylation of the retinoblastoma protein. Substrate phosphorylation releases the E2F transcription factor which in turn regulates the expression of genes required for S phase entry. Inhibition of these kinases, therefore, blocks cell entry into the S phase and downstream proliferative events.

Small molecular cyclin dependent kinase inhibitors have already been identified and shown to have growth inhibitory activity against a number of different tumor types *in vitro* and *in vivo*. Glab, N. et al. (1994) *FEBS Lett.* 353, 207-211, Kitagawa, M. et al. (1993) *Oncogene* 8, 2425-2432, Losiewicz, M.D. et al. (1994) *Biochem. Biophys. Res. Commun.* 201, 589-595, Carlson, B.A. et al. (1996) *Cancer Res.* 56, 2973-2978, Kelland, L.R. (2000) *Expert Opin. Invest. Drugs* 9, 2903-2911 and Senderowicz, A.M. (1999) *Invest. New Drugs* 17, 313-320.

Accordingly, the identification of small compounds which specifically inhibit, regulate and/or modulate the signal transduction of kinases is desirable and is an object of this invention.

SUMMARY OF THE INVENTION

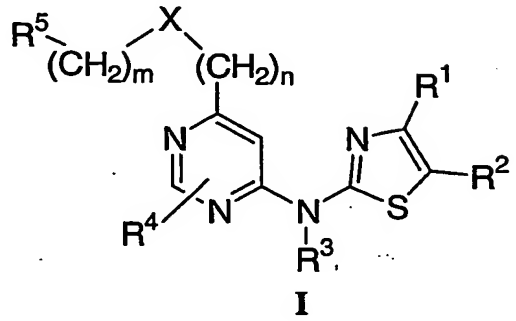
The present invention relates to compounds that are capable of inhibiting, modulating and/or regulating signal transduction of kinases. One embodiment of the present invention is illustrated by a compound of Formula I, and the pharmaceutically acceptable salts and stereoisomers thereof:



I

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of kinases and are illustrated by a compound of Formula I:



I

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein

X is O, S or NR^3;

m is 0, 1, 2 or 3;

n is 0, 1, 2 or 3;

R^1 is:

1) H,
2) $O_r(C_1\text{-}C_6)$perfluoroalkyl,
3) OH,
4) CN,
5) halogen,
6) $(C{=}O)_rO_s(C_1\text{-}C_{10})$alkyl,
7) $(C{=}O)_rO_s(C_2\text{-}C_{10})$alkenyl,
8) $(C{=}O)_rO_s(C_2\text{-}C_{10})$alkynyl,
9) $(C{=}O)_rO_s$aryl,
10) $(C{=}O)_rO_s$heterocyclyl, or
11) $(C_0\text{-}C_6)$alkyl-NR^aR^b,

wherein r and s are independently 0 or 1, and said alkyl, alkenyl, alkynyl, aryl and heterocyclyl is optionally substituted with one or more substituents selected from R^6;

R^2 is:

1) H,
2) $O_r(C_1\text{-}C_6)$perfluoroalkyl,
3) OH,
4) CN,
5) halogen,
6) $(C{=}O)_rO_s(C_1\text{-}C_{10})$alkyl,
7) $(C{=}O)_rO_s(C_2\text{-}C_{10})$alkenyl,
8) $(C{=}O)_rO_s(C_2\text{-}C_{10})$alkynyl,
9) $(C{=}O)_rO_s$aryl,
10) $(C{=}O)_rO_s$heterocyclyl, or
11) $(C_0\text{-}C_6)$alkyl-NR^aR^b,

wherein r and s are independently 0 or 1, and said alkyl, alkenyl, alkynyl, aryl and heterocyclyl is optionally substituted with one or more substituents selected from R^6;

R^3 is:

1) H,
2) SO_2R^c,
3) $(C{=}O)_rR^c$, wherein r is 0 or 1, or
4) CO_2R^c;

R^4 is:

1) H,
2) $O_r(C_1\text{-}C_6)$perfluoroalkyl,
3) OH,
4) CN,
5) halogen,
6) $(C{=}O)_rO_s(C_1\text{-}C_{10})$alkyl,
7) $(C{=}O)_rO_s(C_2\text{-}C_{10})$alkenyl,
8) $(C{=}O)_rO_s(C_2\text{-}C_{10})$alkynyl,
9) $(C{=}O)_rO_s$aryl,
10) $(C{=}O)_rO_s$heterocyclyl, or
11) $(C_0\text{-}C_6)$alkyl-NR^aR^b,

wherein r and s are independently 0 or 1, and said alkyl, alkenyl, alkynyl, aryl and heterocyclyl is optionally substituted with one or more substituents selected from R^6;

R^5 is heterocyclyl wherein said heterocyclyl contains one or two heteroatoms selected from N, O and S, and is optionally substituted with one or more substituents selected from R^6;

R^6 is:

1) $O_r(C=O)_sNR^aR^b$,
2) $(C=O)_rO_s$aryl,
3) $(C=O)_rO_s$-heterocyclyl,
4) halogen,
5) OH,
6) oxo,
7) $O(C_1\text{-}C_3)$perfluoroalkyl,
8) $(C_1\text{-}C_3)$perfluoroalkyl,
9) $(C=O)_rO_s(C_1\text{-}C_{10})$alkyl,
10) CHO,
11) CO_2H, or
12) CN,

wherein r and s are independently 0 or 1, and said alkyl, aryl and heterocyclyl are optionally substituted with one or more substituents selected from R^d;

R^a and R^b are independently:

1) H,
2) $(C=O)_r(C_1\text{-}C_{10})$alkyl,
3) $S(O)_2R^c$,
4) $(C=O)_r$heterocyclyl,
5) $(C=O)_r$aryl, or
6) CO_2R^c,

wherein r is 0 or 1 and said alkyl, heterocyclyl, and aryl optionally substituted with one or more substituents selected from R^d, or

R^a and R^b are taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one or more substituents selected from R^d;

R^c is $(C_1\text{-}C_6)$alkyl, aryl, benzyl, or heterocyclyl;

R^d is:

1) $(C{=}O)_rO_s(C_1\text{-}C_{10})$alkyl, wherein r and s are independently 0 or 1, optionally substituted with up to three substituents selected from OH, $(C_1\text{-}C_6)$alkoxy, halogen, CN, oxo, $N(R^e)_2$ and $S(O)_2R^c$,
2) $(C{=}O)N(R^e)_2$,
3) $O_r(C_1\text{-}C_3)$perfluoroalkyl,
4) $(C_0\text{-}C_6)$alkylene-$S(O)_mR^c$, wherein m is 0, 1, or 2,
5) oxo,
6) OH,
7) halogen,
8) CN,
9) $(C_0\text{-}C_6)$alkylene-aryl, optionally substituted with up to three substituents selected from R^e,
10) $(C_0\text{-}C_6)$alkylene-heterocyclyl, optionally substituted with up to three substituents selected from R^e,
11) $(C_0\text{-}C_6)$alkylene-$N(R^e)_2$,
12) $C(O)R^c$,
13) CO_2R^c,
14) C(O)H, or
15) CO_2H; and

R^e is H, $(C_1\text{-}C_6)$alkyl, aryl, heterocyclyl or $S(O)_2R^c$.

A further embodiment is illustrated by a compound as described directly above of Formula I, wherein R^1 is H, CN, halogen, OH, $(C{=}O)_rO_s(C_1\text{-}C_{10})$ alkyl and $(C{=}O)_rO_s(C_1\text{-}C_{10})$alkyl-$NR^aR^b$.

A further embodiment is illustrated by a compound as described directly above of Formula I, wherein R^2 is H, CN, OH, halogen, phenyl, wherein said phenyl is optionally substituted with one or more substituents selected from R^6, $(C{=}O)_rO_s(C_1\text{-}C_{10})$alkyl and $(C{=}O)_rO_s(C_1\text{-}C_{10})$alkyl-$NR^aR^b$.

A further embodiment is illustrated by a compound as described directly above of Formula I, wherein R^4 is H, CN, halogen, phenyl, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$perfluoroalkyl and $(C{=}O)_rO_s$heterocyclyl.

Another embodiment is illustrated by a compound of Formula I described directly above wherein R^1 is H; R^2 is CN or phenyl, R^3 is H, and R^4 is H or $(C_1$-$C_6)$alkyl.

A preferred embodiment is a compound selected from:

tert-butyl-4-({6-[(5-cyano-1,3-thiazol-2-yl)amino]pyrimidin-4-yl}oxy)piperidine-1-carboxylate;

2-{[6-(piperidin-4-yloxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile;

tert-butyl-4-({6-[5-phenyl-1,3-thiazol-2-yl)amino]pyrimidin-4-yl}oxy)piperidine-1-carboxylate;

N-(5-phenyl-1,3-thiazol-2-yl)-6-(piperidin-4-yloxy)pyrimidin-4-amine;

tert-butyl-4-[({6-[5-cyano-1,3-thiazol-2-yl)amino]pyrimidin-4-yl}oxy)methyl]-piperidine-1-carboxylate;

tert-butyl-4-[({6-[(5-phenyl-1,3-thiazol-2-yl)amino]pyrimidin-4-yl}oxy)methyl]-piperidine-1-carboxylate;

N-(5-phenyl-1,3-thiazol-2-yl)-6-(piperidin-4-ylmethoxy)pyrimidin-4-amine;

2-{[2-methyl-6-(piperidin-4-yloxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile;

N-(5-phenyl-1,3-thiazol-2-yl)-6-(piperidin-4-yloxy)-2-methylpyrimidin-4-amine;

2-({2-methyl-6-[(3R)-pyrrolidin-3-yloxy]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile;

2-({2-methyl-6-[(3S)-pyrrolidin-3-yloxy]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile;

2-[2-methyl-6-{[1-(2-morpholin-4-ylethyl)piperidin-4-yl]oxy}pyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile;

2-[4-({6-[5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}oxy)piperidin-1-yl]-N-isopropylacetamide;

2-{[2-methyl-6-(3-morpholin-4-ylpropoxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile;

2-{[2-methyl-6-(2-morpholin-4-ylethoxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile;

2-{[2-methyl-6-(2-piperidin-1-ylethoxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile;

2-({2-methyl-6-[(2-morpholin-4-ylethyl)amino]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile;

2-{[6-(piperidin-4-ylmethoxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile;

2-{[2-methyl-6-(piperidin-4-ylmethoxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile;

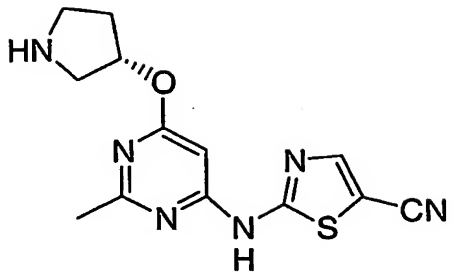
2-({6-[(3-morpholin-4-ylpropyl)amino]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile;

2-{[2-methyl-6-(tetrahydro-2H-pyran-4-ylamino)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile;

2-[(6-{[3-(1H-imidazol-1-yl)propyl]amino}-2-methylpyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile;

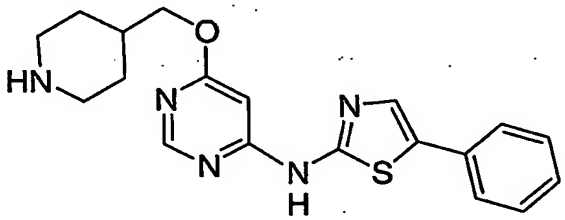
2-[(6-{[(1,1-dioxidotetrahyrothien-3ylmethyl]amino}-2-methylpyrimidin-4-yl) amino]-1,3-thiazole-5-carbonitrile;
2-({6-[(1,4-dioxan-2-ylmethyl)amino]-2-methylpyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile;
(3-morpholin-4-ylpropyl)amino]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile;
[5-cyano-1,3-thiazol-2-ylamino]-2-methylpyrimidin-4-yl}amino)piperidin-1-yl]-N-isopropylacetamide;
tyl-4-({6-[(5-cyano-1,3-thiazol-2-ylamino]-2-methylpyrimidin-4-yl}amino) piperidine-1-late;
methyl-6-(piperidin-4-ylamino)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile;
tert-butyl-4-({6-[(5-cyano-1,3-thiazol-2-yl)amino]methyl}-2-methylpyrimidin-4-yl} amino) piperidine-1-carboxylate;
2-({2-methyl-6-[(piperidin-4-ylmethyl)amino]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile;
2-{[5-methyl-6-(piperidin-4-ylamino)pyrimidin-4-yl]oxy}-1,3-thiazole-5-carbonitrile;
tert-butyl-2-[({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}oxy) methyl]-morpholine-4-carboxylate;
2-{[2-methyl-6-(morpholin-2-ylmethoxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile;
2-{[2-methyl-6-(tetrahydro-2-pyran-4-yloxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile;
2-{[2-isopropyl-6-(piperidin-4-yloxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile;
2-({6-[(1,1-dioxidotetrahydrothien-3-yl)amino]-2-methylpyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile;
2-{[2-methyl-6-(tetrahydrofuran-3-ylamino)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile;
tert-butyl{4-[({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}oxy) methyl]piperidin-1-yl}acetate;
{4-[({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}oxy)methyl] piperidin-1-yl}acetic acid;
N-(tert-butyl)-2-{4-[({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl} oxy)methyl]piperidin-1-yl}acetamide;
2-({2-methyl-6-[(2-morpholin-4-ylethyl)thio]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile;
and
2-{[6-(piperidin-4-ylthio)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile;
or a pharmaceutically acceptable salt or stereoisomer thereof.

Yet another embodiment of the present invention is a compound which is: 2-({2-methyl-6-[(3S)-pyrrolidin-3-yloxy]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile



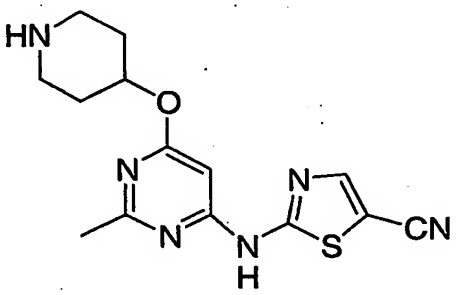
or a pharmaceutically acceptable salt or stereoisomer thereof.

Another embodiment of the present invention is a compound which is: N-(5-phenyl-1,3-thiazol-2-yl)-6-(piperidin-4-yloxy)pyrimidin-4-amine



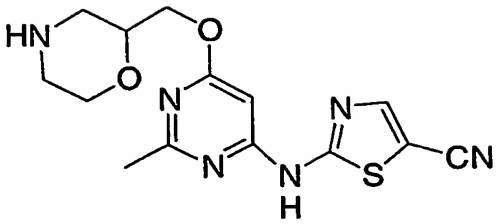
or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is a compound which is2-{[2-methyl-6-(piperidin-4-yloxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile



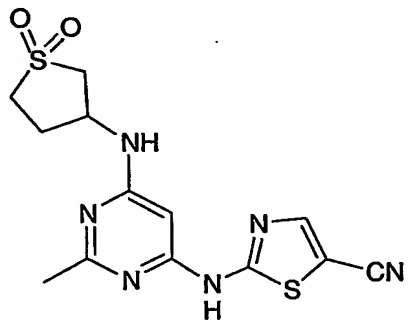
or a pharmaceutically acceptable salt thereof.

And yet another embodiment of the present invention is a compound which is 2-{[2-methyl-6-(morpholin-2-ylmethoxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile



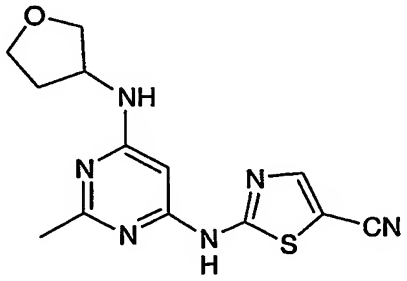
or a pharmaceutically acceptable salt or stereoisomer thereof.

Another embodiment of the present invention is a compound which is 2-({6-[(1,1-dioxidotetrahydrothien-3-yl)amino]-2-methylpyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile



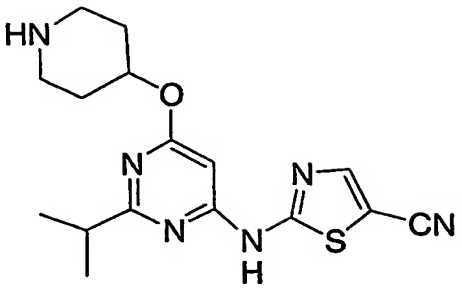
or a pharmaceutically acceptable salt or stereoisomer thereof.

In yet another embodiment of the present invention is a compound which is 2-{[2-methyl-6-(tetrahydrofuran-3-ylamino)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile



or a pharmaceutically acceptable salt or stereoisomer thereof.

Another embodiment of the present invention is a compound which is 2-{[2-isopropyl-6-(piperidin-4-yloxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile



or a pharmaceutically acceptable salt thereof.

Also included within the scope of the present invention is a pharmaceutical composition which is comprised of a compound of Formula I as described above and a pharmaceutically acceptable carrier. The invention is also contemplated to encompass a pharmaceutical composition which is comprised of a pharmaceutically acceptable carrier and any of the compounds specifically disclosed in the present application. These and other aspects of the present invention will be apparent from the teachings contained herein.

Utilities

The compounds of the present invention are inhibitors of kinases and are therefore useful to treat or prevent kinase-dependent diseases or conditions in mammals.

"Tyrosine kinase-dependent diseases or conditions" refers to pathologic conditions that depend on the activity of one or more tyrosine kinases. Tyrosine kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion and migration, and differentiation. Diseases associated with tyrosine kinase activities include the proliferation of tumor cells, the pathologic neovascularization that supports solid tumor growth, ocular neovascularization (diabetic retinopathy, age-related macular degeneration, retinal ischemia, macular edema and the like) and inflammation (psoriasis, rheumatoid arthritis, and the like). In treating such conditions with the instantly claimed compounds, the required therapeutic amount will vary according to the specific disease and is readily ascertainable by those skilled in the art. Although both treatment and prevention are contemplated by the scope of the invention, the treatment of these conditions is the preferred use.

The present invention encompasses a method of treating or preventing cancer in a mammal in need of such treatment which is comprised of administering to said mammal a therapeutically effective amount of a claimed compound. Preferred cancers for treatment are selected from cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung. Another set of preferred forms of cancer are histiocytic lymphoma, lung adenocarcinoma,

small cell lung cancers, pancreatic cancer, glioblastomas and breast carcinoma. A further preferred group of cancers for treatment with the present compounds is a cancer selected from lung cancer, prostate cancer, breast cancer and colorectal cancer. The utility of angiogenesis inhibitors in the treatment of cancer is known in the literature, see J. Rak et al. *Cancer Research*, 55:4575-4580, 1995, for example. The role of angiogenesis in cancer has been shown in numerous types of cancer and tissues: breast carcinoma (G. Gasparini and A.L. Harris, *J. Clin. Oncol.*, 1995, 13:765-782; M. Toi et al., *Japan. J. Cancer Res.*, 1994, 85:1045-1049); bladder carcinomas (A.J. Dickinson et al., *Br. J. Urol.*, 1994, 74:762-766); colon carcinomas (L.M. Ellis et al., *Surgery*, 1996, 120(5):871-878); and oral cavity tumors (J.K. Williams et al., *Am. J. Surg.*, 1994, 168:373-380).

Tumors which have undergone neovascularization show an increased potential for metastasis. VEGF released from cancer cells enhances metastasis possibly by increasing extravasation at points of adhesion to vascular endothelium. (A. Amirkhosravi et al., *Platelets*, 10:285-292 (1999)). In fact, angiogenesis is essential for tumor growth and metastasis. (S.P. gunningham, et al., *Can. Research*, 61: 3206-3211 (2001)). The angiogenesis inhibitors disclosed in the present application are therefore also useful to prevent or decrease tumor cell metastasis. Such a use is also contemplated to be within the scope of the present invention.

Further included within the scope of the invention is a method of treating or preventing a disease in which angiogenesis is implicated, which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the present invention. Ocular neovascular diseases are an example of conditions where much of the resulting tissue damage can be attributed to aberrant infiltration of blood vessels in the eye (see WO 00/30651, published 2 June 2000). The undesireable infiltration can be triggered by ischemic retinopathy, such as that resulting from diabetic retinopathy, retinopathy of prematurity, retinal vein occlusions, etc., or by degenerative diseases, such as the choroidal neovascularization observed in age-related macular degeneration. Inhibiting the growth of blood vessels by administration of the present compounds would therefore prevent the infiltration of blood vessels and prevent or treat diseases where angiogenesis is implicated, such as ocular diseases like retinal vascularization, diabetic retinopathy, retinal ischemia, macular edema, age-related macular degeneration, and the like.

Also included within the scope of the present invention is a method of treating or preventing inflammatory diseases which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formual I. Examples of such inflammatory diseases are rheumatoid arthritis, psoriasis, contact dermatitis, delayed hypersensitivity reactions, and the like. (A. Giatromanolaki et al., *J. Pathol.* 2001; 194:101-

108.) For the role of VEGF in skin angiogenesis, see Michael Detmar, *J. Dermatological Sci.*, 24 Suppl. 1, S78-S84 (2000).

Also included within the scope of the present invention is a method of treating or preventing bone associated pathologies selected from osteosarcoma, osteoarthritis, and rickets, also known as oncogenic osteomalacia. (Hasegawa et al., *Skeletal Radiol.*, *28*, pp.41-45, 1999; Gerber et al., *Nature Medicine*, Vol. 5, No. 6, pp.623-628, June 1999.) And since VEGF directly promotes osteoclastic bone resorption through KDR/Flk-1 expressed in mature osteoclasts (FEBS Let. 473:161-164 (2000); *Endocrinology*, 141:1667 (2000)), the instant compounds are also useful to treat and prevent conditions related to bone resorption, such as osteoporosis and Paget's disease.

A method of treating or preventing preeclampsia is also within the scope of the present invention, which comprises administering a therapeutically effective amount of a compound of Formula I. Studies have shown that the action of VEGF on the Flt-1 receptor is pivotal in the pathogenesis of preeclampsia. (*Laboratory Investigation* 79:1101-1111 (September 1999)). Vessels of pregnant women incubated with VEGF exhibit a reduction in endothelium-dependent relaxation similar to that induced by plasma from women with preeclampsia. In the presence of an anti-Flt-1 receptor antibody, however, neither VEGF or plasma from women with preeclampsia reduced the endothelium-dependent relaxation. Therefore the claimed compounds serve to treat preeclampsia via their action on the tyrosine kinase domain of the Flt-1 receptor.

Also within the scope of the invention is a method of reducing or preventing tissue damage following a cerebral ischemic event which comprises administering a therapeutically effective amount of a compound of the present invention. The claimed compounds can also be used to reduce or prevent tissue damage which occurs after cerebral ischemic events, such as stroke, by reducing cerebral edema, tissue damage, and reperfusion injury following ischemia. (*Drug News Perspect* 11:265-270 (1998); *J. Clin. Invest.* 104:1613-1620 (1999); *Nature Med* 7:222-227 (2001)).

The instant compounds can also be used to prevent or treat tissue damage during bacterial meningitis, such as tuberculous meningitis. (Matsuyama et al., *J. Neurol. Sci.* 186:75-79 (2001)). The instant invention therefore encompasses a method of treating or preventing tissue damage due to bacterial meningitis which comprises administering a therapeutically effective amount of a claimed compound. Studies have shown that VEGF is secreted by inflammatory cells during bacterial meningitis and that VEGF contributes to blood-brain barrier disruption. (van der Flier et al., *J. Infectious Diseases*, 183:149-153 (2001)). The claimed

compounds can inhibit VEGF-induced vascular permeability and therefore serve to prevent or treat blood-brain barrier disruption associated with bacterial meningitis.

The present invention further encompasses a method to treat or prevent endometriosis comprised of administering a therapeutically effective amount of a claimed compound. An increase in VEGF expression and angiogenesis is associated with the progression of endometriosis (Stephen K. Smith, *Trends in Endocrinology & Metabolism*, Vol. 12 No. 4, May/June 2001). Inhibition of VEGF by the current compounds would therefore inhibit angiogenesis and treat endometriosis.

A further embodiment of the present invention is a method of treating acute myeloid leukemia (AML) which comprises administering a therapeutically effective amount of a claimed compound. Activation of FLT3 on leukemic cells by FLT3 ligand leads to receptor dimerization and signal transduction in pathways that promote cell growth and inhibit apoptosis (*Blood*, Vol. 98, No. 3, pp.885-887 (2001)). The present compounds are therefore useful to treat AML via inhibition of the tyrosine kinase domain of Flt-3.

Another embodiment of the present invention is a method of treating or preventing cancer via the dual inhibition of cyclin dependent kinase and tyrosine kinase. Cyclin dependent kinases are known to regulate cell cycle progression and cyclin dependent kinase inhibitors have been shown to block cell proliferation. As described above, inhibition of tyrosine kinases is useful in the treatment and prevention of cancer. Furthermore, inhibition of cyclin dependant kinases is also useful in the treatment and prevention of cancer (Glab et al., *FEBS Lett.* 353, 207-211 (1994), Kitagawa et al., *Oncogene*. 8, 2425-2432 (1993), Losiewicz et al., *Biochem. Biophys. Res. Commun.* 201, 589-595 (1994), Carlson et al. *Cancer Res.* 56, 2973-2978 (1996), Kelland, L.R. *Expert Opin. Invest. Drugs*. 9, 2903-2911 (2000) and Senderowicz, A.M. *Invest. New Drugs*. 17, 313-320 (1999)). Thus, dual inhibition of two separate signaling pathways provides an advantage in the inhibition of cell proliferation and cancer progression. The present compounds demonstrate dual inhibitory activity against cyclin dependent kinases as well as tyrosine kinases and are therefore useful in the treatment and prevention of cancer.

The present invention encompasses a method of treating or preventing cancer via the dual inhibition of tyrosine kinase and cyclin dependent kinase wherein the dual inhibitor is selected from:

tert-butyl{4-[({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}oxy) methyl]piperidin-1-yl}acetate;

2-{[2-methyl-6-(piperidin-4-yloxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile;

2-{[2-methyl-6-(piperidin-4-ylmethoxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile; and

2-{[2-isopropyl-6-(piperidin-4-yloxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile;

or a pharmaceutically acceptable salt thereof.

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use of a chemotherapeutic compound according to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and cornstarch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The instant compounds are also useful in combination with known anti-cancer agents. Combinations of the presently disclosed compounds with other anti-cancer or chemotherapeutic agents are within the scope of the invention. Examples of such agents can be found in *Cancer Principles and Practice of Oncology* by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such anti-cancer agents include the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors. The instant compounds are particularly useful when coadminsitered with radiation therapy. The synergistic effects of inhibiting VEGF in combination with radiation therapy have been described in the art (see WO 00/61186). The use of angiogenesis inhibitors with other chemotherapeutic agents is especially desirable since the normalization of tumor vasculature improves the delivery of the other therapeutic agents. (*Nature Medicine*, Vol. 7, No. 9, pp. 987-989 (September 2001)).

"Estrogen receptor modulators" refers to compounds which interfere or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate. For an example of a previously reported combination of an androgen receptor modulator (a non-steroidal anti-androgen, in this case) and a tyrosine kinase inhibitor, see WO 0176586, published on 18 October 2001.

"Retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

"Cytotoxic agents" refer to compounds which cause cell death primarily by interfering directly with the cell's functioning or inhibit or interfere with cell myosis, including alkylating agents, tumor necrosis factors, intercalators, microtubulin inhibitors, and topoisomerase inhibitors.

Examples of cytotoxic agents include, but are not limited to, tirapazimine, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032).

Examples of microtubulin inhibitors include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin

isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, and BMS188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexohydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c] quinolin-7-one, and dimesna.

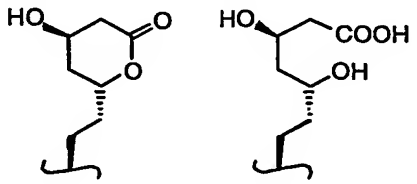
"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone.

"Antiproliferative agents" also includes monoclonal antibodies to growth factors, other than those listed under "angiogenesis inhibitors", such as trastuzumab, and tumor suppressor genes,

such as p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Patent No. 6,069,134, for example).

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33. The terms "HMG-CoA reductase inhibitor" and "inhibitor of HMG-CoA reductase" have the same meaning when used herein.

Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Patent Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Patent Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896), atorvastatin (LIPITOR®; see U.S. Patent Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952) and cerivastatin (also known as rivastatin and BAYCHOL®; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention. An illustration of the lactone portion and its corresponding open-acid form is shown below as structures I and II.



Lactone I Open-Acid II

In HMG-CoA reductase inhibitors where an open-acid form can exist, salt and ester forms may preferably be formed from the open-acid, and all such forms are included within the meaning of the term "HMG-CoA reductase inhibitor" as used herein. Preferably, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin, and most preferably

simvastatin. Herein, the term "pharmaceutically acceptable salts" with respect to the HMG-CoA reductase inhibitor shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenz-imidazole, diethylamine, piperazine, and tris(hydroxymethyl) aminomethane. Further examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

Ester derivatives of the described HMG-CoA reductase inhibitor compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

"Prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). Examples of prenyl-protein transferase inhibiting compounds include (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, (-)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl) methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, 5(S)-n-butyl-1-(2,3-dimethylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, (S)-1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl) methyl)-2-piperazinone, 5(S)-n-Butyl-1-(2-methylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, 1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-2-piperazinone, 1-(2,2-diphenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]piperidine, 4-{5-[4-hydroxymethyl-4-(4-

chl...opyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl} benzonitrile, 4-{5-[4-hydroxymethyl-4-(3-chlorobenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile, 4-{3-[4-(2-oxo-2H-pyridin-1-yl)benzyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(5-chloro-2-oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-...l}benzonitrile, 4-{3-[4-(2-oxo-2H-[1,2'] bipyridin-5'-ylmethyl]-3H-imidazol-4-...yl}benzonitrile, 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl}benzonitrile, 18,19-dihydro-19-oxo-5*H*,17*H*-6,10:12,16-dimetheno-1H-imidazo[4,3-...4]dioxaazacyclo-nonadecine-9-carbonitrile, (±)-19,20-dihydro-19-oxo-5*H*-18,21-ethano-...theno-6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxatriaza-cyclooctadecine-9-...nitrile, 19,20-dihydro-19-oxo-5*H*,17*H*-18,21-ethano-6,10:12,16-dimetheno-22*H*-...imidazo[3,4-*h*][1,8,11,14]oxatriazacycloeicosine-9-carbonitrile, and (±)-19,20-dihydro-3-methyl-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo [*d*]imidazo[4,3-*k*][1,6,9,12]oxa-triazacyclooctadecine-9-carbonitrile.

Other examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Patent No. 5,420,245, U.S. Patent No. 5,523,430, U.S. Patent No. 5,532,359, U.S. Patent No. 5,510,510, U.S. Patent No. 5,589,485, U.S. Patent No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Patent No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Patent No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Patent No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see *European J. of Cancer*, Vol. 35, No. 9, pp.1394-1401 (1999).

Examples of HIV protease inhibitors include amprenavir, abacavir, CGP-73547, CGP-61755, DMP-450, indinavir, nelfinavir, tipranavir, ritonavir, saquinavir, ABT-378, AG 1776, and BMS-232,632. Examples of reverse transcriptase inhibitors include delaviridine, efavirenz, GS-840, HB Y097, lamivudine, nevirapine, AZT, 3TC, ddC, and ddI.

"Angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-α, interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxy-genase-2 inhibitors like celecoxib and rofecoxib (*PNAS*, Vol. 89, p. 7384 (1992); *JNCI*, Vol. 69, p. 475 (1982); *Arch. Opthalmol.*, Vol. 108, p.573 (1990); *Anat. Rec.*, Vol. 238, p. 68 (1994); *FEBS Letters*, Vol. 372, p. 83 (1995); *Clin. Orthop.* Vol. 313, p. 76 (1995); *J. Mol. Endocrinol.*, Vol. 16, p.107 (1996); *Jpn. J. Pharmacol.*, Vol. 75, p. 105 (1997); *Cancer Res.*, Vol. 57, p. 1625 (1997); *Cell*, Vol. 93, p. 705 (1998); *Intl. J. Mol. Med.*, Vol. 2, p. 715 (1998); *J. Biol. Chem.*, Vol. 274, p. 9116 (1999)), steroidal anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez et al., *J. Lab. Clin. Med.* 105:141-145 (1985)), and antibodies to VEGF (see, *Nature Biotechnology*, Vol. 17, pp.963-968 (October 1999); Kim et al., *Nature*, *362*, 841-844 (1993); WO 00/44777; and WO 00/61186).

Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the salts of the instant invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review in *Clin. Chem. La. Med.* 38:679-692 (2000)). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see *Thromb. Haemost.* 80:10-23 (1998)), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see *Thrombosis Res.* 101:329-354 (2001)). TAFIa inhibitors have been described in U.S. Ser. Nos. 60/310,927 (filed August 8, 2001) and 60/349,925(filed January 18, 2002).

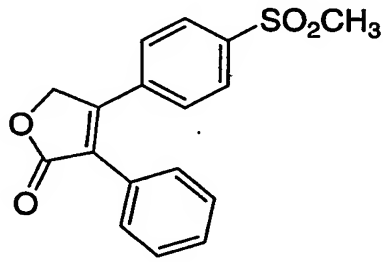
As described above, the combinations with NSAID's are directed to the use of NSAID's which are potent COX-2 inhibiting agents. For purposes of this specification an NSAID is potent if it possesses an IC_{50} for the inhibition of COX-2 of 1μM or less as measured by cell or microsomal assays.

The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at

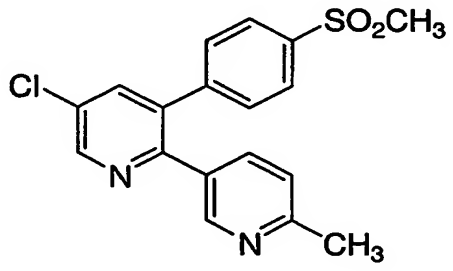
least 100 fold as measured by the ratio of IC_{50} for COX-2 over IC_{50} for COX-1 evaluated by cell or microsomal assays. Such compounds include, but are not limited to those disclosed in U.S. Patent 5,474,995, issued December 12, 1995, U.S. Patent 5,861,419, issued January 19, 1999, U.S. Patent 6,001,843, issued December 14, 1999, U.S. Patent 6,020,343, issued February 1, 2000, U.S. Patent 5,409,944, issued April 25, 1995, U.S. Patent 5,436,265, issued July 25, 1995, U.S. Patent 5,536,752, issued July 16, 1996, U.S. Patent 5,550,142, issued August 27, 1996, U.S. Patent 5,604,260, issued February 18, 1997, U.S. 5,698,584, issued December 16, 1997, U.S. Patent 5,710,140, issued January 20, 1998, WO 94/15932, published July 21, 1994, U.S. Patent 5,344,991, issued June 6, 1994, U.S. Patent 5,134,142, issued July 28, 1992, U.S. Patent 5,380,738, issued January 10, 1995, U.S. Patent 5,393,790, issued February 20, 1995, U.S. Patent 5,466,823, issued November 14, 1995, U.S. Patent 5,633,272, issued May 27, 1997, and U.S. Patent 5,932,598, issued August 3, 1999, all of which are hereby incorporated by reference.

Inhibitors of COX-2 that are particularly useful in the instant method of treatment are:

3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone; and



5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine;

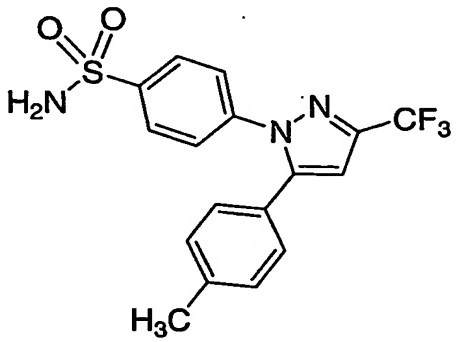


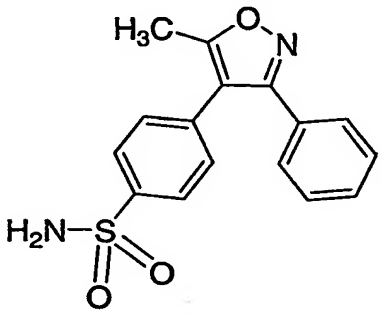
or a pharmaceutically acceptable salt thereof.

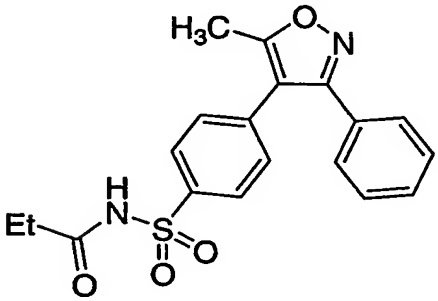
General and specific synthetic procedures for the preparation of the COX-2 inhibitor compounds described above are found in U.S. Patent No. 5,474,995, issued December

12, 1995, U.S. Patent No. 5,861,419, issued January 19, 1999, and U.S. Patent No. 6,001,843, issued December 14, 1999, all of which are herein incorporated by reference.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to, the following:







or a pharmaceutically acceptable salt thereof.

Compounds which are described as specific inhibitors of COX-2 and are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference: WO 94/15932, published July 21, 1994, U.S. Patent No. 5,344,991, issued June 6, 1994, U.S. Patent No. 5,134,142, issued July 28, 1992, U.S. Patent No. 5,380,738, issued

January 10, 1995, U.S. Patent No. 5,393,790, issued February 20, 1995, U.S. Patent No. 5,466,823, issued November 14, 1995, U.S. Patent No. 5,633,272, issued May 27, 1997, and U.S. Patent No. 5,932,598, issued August 3, 1999.

Compounds which are specific inhibitors of COX-2 are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference: U.S. Patent No. 5,474,995, issued December 12, 1995, U.S. Patent No. 5,861,419, issued January 19, 1999, U.S. Patent No. 6,001,843, issued December 14, 1999, U.S. Patent No. 6,020,343, issued February 1, 2000, U.S. Patent No. 5,409,944, issued April 25, 1995, U.S. Patent No. 5,436,265, issued July 25, 1995, U.S. Patent No. 5,536,752, issued July 16, 1996, U.S. Patent No. 5,550,142, issued August 27, 1996, U.S. Patent No. 5,604,260, issued February 18, 1997, U.S. Patent No. 5,698,584, issued December 16, 1997, and U.S. Patent No. 5,710,140, issued January 20,1998.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide,CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonyl-imino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-

kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

The instant compounds are also useful, alone or in combination with platelet fibrinogen receptor (GP IIb/IIIa) antagonists, such as tirofiban, to inhibit metastasis of cancerous cells. Tumor cells can activate platelets largely via thrombin generation. This activation is associated with the release of VEGF. The release of VEGF enhances metastasis by increasing extravasation at points of adhesion to vascular endothelium (Amirkhosravi, *Platelets* 10, 285-292, 1999). Therefore, the present compounds can serve to inhibit metastasis, alone or in combination with GP IIb/IIIa antagonists. Examples of other fibrinogen receptor antagonists include abciximab, eptifibatide, sibrafiban, lamifiban, lotrafiban, cromofiban, and CT50352.

Combinations with compounds other than anti-cancer compounds are also encompassed to treat conditions other than cancer. For example, combinations of the instantly claimed compounds with PPAR-γ (i.e., PPAR-gamma) agonists are useful in the treatment of diabetic retinopathy. PPAR-γ is the nuclear peroxisome proliferator-activated receptor γ. The expression of PPAR-γ on endothelial cells and its involvement in angiogenesis in corneal and choroidal experimental systems has been reported in the literature (see *J. Cardiovasc. Pharmacol.* 1998; 31:909-913; *J. Biol. Chem.* 1999; 274:9116-9121; *Invest. Ophthalmol Vis. Sci.* 2000; 41:2309-2317). More recently, PPAR-γ agonists have been shown to inhibit the angiogenic response to VEGF *in vitro*; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice. (*Arch. Ophthamol.* 2001; 119:709-717). Examples of PPAR-γ aganoists and PPAR-γ/α aganoists include, but are not limited to, thiazolidinediones (such as DRF2725, CS-011, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622, GI262570, PNU182716, DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid (disclosed in USSN 09/782,856), and 2(R)-7-(3-(2-chloro-4-(4-fluorophenoxy) phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid (disclosed in USSN 60/235,708 and 60/244,697). Thus, a method of treating or preventing diabetic retinopathy which comprises administering a therapeutically effective amount of a claimed compound in combination with a PPAR-γ agonist is also within the scope of the present invention.

Another aspect of the invention is illustrated by a composition comprising a therapeutically effective amount of the disclosed kinase inhibitors and a steroidal

anti-inflammatory. Steroidal anti-inflammatories include, but are not limited to, corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, and betamethasone. This combination is particularly useful in ophthalmic formulations which may, in some cases, be associated with irritation of the ocular tissues.

A particularly useful combination for the treatment of diseases wherein aberrant angiogenesis is present involves administering a therapeutically effective amount of the instantly disclosed kinase inhibiting compounds in combination with photodynamic therapy and a photosensitive drug such as verteoporfin (BPD-MA) (Carruth, Clinical Applications of Photodynamic Therapy, *Int. J. Clin. Pract.* 1998; 52(1):39-42). Such diseases include, but are not limited to, age-related macular degeneration (Bressler, Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Investigation Using Verteoporfin, *Invest. Ophthalmol. Vis. Sci.* 1998; 39 S242), cancer, especially melanoma and non-melanoma skin cancer, including basal cell and squamous cell carcinomas, (Hassan and Parrish, Photodynamic Therpay in Cancer, *Cancer Med.* 1997; Dougherty et al., Photodynamic Therapy for the Treatment of Cancer: Current Status and Advances in Photodynamic Therapy of Neoplastic Disease. Kessel (Ed.), CRC Press, 1989; 1-19); Dougherty et al., Photodynamic Therpay, *J. Natl. Cancer Inst.*, 1998, 90(12): 889-905; Jori, Factors Controlling the Selectivity and Efficiency of Tumour Damage in Photodynamic Therapy, *Laser Med. Sci.* 1990; 5: 115-120; Zhou, Mechanism of Tumour Necrosis Induced by Photodynamic Therapy, *J. Photochem. Photobiol.* 1989; 3: 299-318), psoriasis (Bissonnette et al., Photodynamic Therapy of Psoriasis and Psoriatic Arthritis with BPD verteporfin. 7th Biennial Congress, International Photodynamic Association, Nantes, France 1998:73), and rheumatoid arthritis (Hendrich et al., Photodynamic Therapy for Rheumatoid Arthritis. *Lasermedizin* 11: 73-77 (1995); Hendrich et al. Photodynamic Laser Therapy for Rheumatoid Arthritis: Cell Culture Studies and Animal Experiments, *Knee Surg. Sports Traumatol. Arthroscopy* 5: 58-63 (1997).

Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with gene therapy for the treatment of cancer. For an overview of genetic strategies to treating cancer see Hall et al (*Am J Hum Genet* 61:785-789, 1997) and Kufe et al (*Cancer Medicine*, 5th Ed, pp 876-889, BC Decker, Hamilton 2000). Gene therapy can be used to deliver any tumor suppresing gene. Examples of such genes include, but are not limited to, p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Patent No. 6,069,134, for example), a uPA/uPAR antagonist ("Adenovirus-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice," *Gene Therapy*, August 1998;5(8):1105-13), and interferon gamma (*J Immunol* 2000;164:217-222).

VEGF receptor tyrosine kinases have been reported to cause a sustained increase in blood pressure in rats when administered more than once, particularly when administered chronically. It is desirable, however, to produce an antiangiogenic effect without causing hypertension. This can be achieved by treating a disease state associated with angiogenesis with a therapeutically effective amount of a combination of an anti-angiogenic agent, such as those presently disclosed, and an anti-hypertensive agent (see WO 01/74360, hereby incorporated by reference). The present invention therefore encompasses a pharmaceutical composition comprising a therapeutically effective amount of a combination of a compound of Formula I and an anti-hypertensive compound.

An anti-hypertensive is any agent which lowers blood pressure. There are numerous categories of anti-hypertensive agents including calcium channel blockers, angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor antagonists (A-II antagonists), diuretics, beta-adrenergic receptor blockers (β-blockers), vasodilators, alpha-adrenergic receptor blockers (α-blockers), selective neutral endopeptidase (NEP) inhibitors and dual ACE-NEP inhibitors. Any anti-hypertensive agent may be used in accordance with this invention and examples from each class are given below.

Calcium channel blockers which are within the scope of this invention include, but are not limited to: amlodipine (U.S. Patent No. 4,5 72,909); bepridil (U.S. Patent No. 3,962,23 8 or U.S. Reissue No. 30,577); clentiazem (U.S. Patent No. 4, 567,175); diltiazem (U.S. Patent No. 3,562,257); fendiline (U.S. Patent No. 3,262,977); gallopamil (U.S. Patent No. 3,261,859); mibefradil (U.S. Patent No. 4,808,605); prenylamine (U.S. Patent No. 3,152,173); semotiadil (U.S. Patent No. 4,786,63 5); terodiline (U.S. Patent No. 3,3 71,014); verapamil (U.S. Patent No. 3,261,859); aranidipine (U.S. Patent No. 4, 446,325); bamidipine (U.S. Patent No. 4,220,649); benidipine (European Patent Application Publication No. 106,275); cilnidipine (U.S. Patent No. 4,672,068); efonidipine (U.S. Patent No. 4,885,284);elgodipine (U.S. Patent No. 4,952,592); felodipine (U.S. Patent No. 4, 264,611); isradipine (U.S. Patent No. 4,466,972); lacidipine (U.S. Patent No. 4,801,599); lercanidipine (U.S. Patent No. 4,705,797); manidipine (U.S. Patent No. 4,892,875); nicardipine (U.S. Patent No. 3,985,758); nifedipine (U.S. Patent No. 3,485,847); nilvadipine (U.S. Patent No. 4,338,322); nimodipine (U.S. Patent No. 3,799,934); nisoldipine (U.S. Patent No. 4,154,83 9); nitrendipine (U.S. Patent No. 3,799,934); cinnarizine (U.S. Patent No. 2,882,271); flunarizine (U.S. Patent No. 3,773,93 9); lidoflazine (U.S. Patent No. 3,267,104); lomerizine (U.S. Patent No. 4,663,325); bencyclane (Hungarian Patent No. 151,865); etafenone (German Patent No. 1,265,758); and perhexiline (British Patent No. 1,025,578). The disclosures of all such patents and patent applications are incorporated herein by reference.

Angiotensin Converting Enzyme Inhibitors (ACE-Inhibitors) which are within the scope of this invention include, but are not limited to: alacepril (U.S. Patent No. 4,248,883); benazepril (U.S. Patent No. 4,410,520); captopril (U.S. Patents Nos. 4, 046,889 and 4,105,776); ceronapril (U.S. Patent No. 4,452,790); delapril. (U.S. Patent No. 4,385,05 1); enalapril (U.S. Patent No. 4,374,829); fosinopril (U.S. Patent No. 4,337,201); imidapril (U.S. Patent No. 4,508,727); lisinopril (U.S. Patent No. 4,555,502); moveltipril (Belgium Patent No. 893,553); perindopril (U.S. Patent No. 4,508,729); quinapril (U.S. Patent No. 4,344,949); ramipril (U.S. Patent No. 4,587,258); spirapril (U.S. Patent No. 4,470,972); temocapril (U.S. Patent No. 4,699,905); and trandolapril (U.S. Patent No. 4,933,361). The disclosures of all such patents are incorporated herein by reference.

Angiotensin-II receptor antagonists (A-II antagonists) which are within the scope of this invention include, but are not limited to: candesartan (U.S. Patent No. 5,196,444); eprosartan (U.S. Patent No. 5,185,351); irbesartan (U.S. Patent No. 5,270,317); losartan (U.S. Patent No. 5,138,069); and valsartan (U.S. PatentNo. 5,399,578. The disclosures of all such U.S. patents are incorporated herein by reference.

β-Blockers which are within the scope of this invention include, but are not limited to: acebutolol (U.S. Patent No. 3,857,952); alprenolol (Netherlands Patent Application No. 6,605,692); amosulalol (U.S. Patent No. 4,217,305); arotinolol (U.S. Patent No. 3,932,400); atenolol (U.S. Patents Nos. 3,663,607 and 3,836,671); befunolol (U.S. Patent No. 3,853,923); betaxolol (U.S. Patent No. 4,252,984); bevantolol (U.S. Patent No. 3,857,891); bisoprolol (U.S. Patent No. 4,258,062); bopindolol (U.S. Patent No. 4,340,541); bucumolol (U.S. Patent No. 3,663,570); bufetolol (U.S. Patent No. 3,723,476); bufuralol (U.S. Patent No. 3,929,836); bunitrolol (U.S. Patent No. 3,541,130); bupranolol (U S. Patent No. 3,309,406); butidrine hydrochloride (French Patent No. 1,390,056); butofilolol (U.S. Patent No. 4,302,601); carazolol (German Patent No. 2,240,599); carteolol (U.S. Patent No. 3,910,924); carvedilol (U.S. PatentNo. 4,503,067); celiprolol (U.S. Patent No. 4,034,009); cetamolol (U.S. Patent No. 4,059,622); cloranolol (German Patent No. 2, 213,044); dilevalol (Clifton et al., *Journal of Medicinal Chemistry*, 1982, 25, 670); epanolol (U.S. Patent No. 4,167,58 1); indenolol (U.S. Patent No. 4,045,482); labetalol (U.S. Patent No. 4,012,444); levobunolol (U.S. Patent No. 4,463,176); mepindolol (Seeman et al, *Helv. Chim. Acta*, 1971, 54, 2411); metipranolol (Czechoslovakian Patent Application No. 128,471); metoprolol (U.S. Patent No. 3,873,600); moprolol (U.S. Patent No. 3,501,769); nadolol (U.S. Patent No. 3,935,267); nadoxolol (U.S. Patent No. 3,819,702); nebivalol (U.S. Patent No. 4,654,3 62); nipradilol (U.S Patent No. 4,394,382); oxprenolol (British Patent No. 1, 077,603); penbutolol (U.S. Patent No. 3,551,493); pindolol (Swiss Patents Nos. 469,002 and 472,404); practolol (U.S. Patent No. 3,408,387);

pronethalol (British Patent No. 909,357); propranolol (U.S. Patents Nos. 3,337,628 and 3,520,919); sotalol (Uloth et al., *Journal of Medicinal Chemistry*, 1966, 9, 88); sulfinalol (German Patent No. 2,728,641); talinolol (U.S. Patents Nos. 3,935,259 and 4,038,313); tertatolol (U.S. Patent No. 3,960,891); tilisolol (U.S. Patent No. 4,129,565); timolol (U.S. Patent No. 3,655,663); toliprolol (U.S. Patent No. 3,432,545); and xibenolol (U.S. Patent No. 4, 018,824). The disclosures of all such patents, patent applications and references are incorporated herein by reference.

α-Blockers which are within the scope of this invention include, but are not limited to: amosulalol (U.S. Patent No. 4,217,305); arotinolol; dapiprazole (U.S. Patent No. 4,252,721); doxazosin (U.S. Patent No. 4,188,390); fenspiride (U.S. Patent No. 3,399,192); indoramin (U.S. Patent No. 3,527,761); labetolol; naftopidil (U.S. Patent No. 3,997,666); nicergoline (U.S. Patent No. 3,228,943); prazosin (U.S. Patent No. 3,511,836); tainsulosin (U.S. Patent No. 4,703,063); tolazoline (U.S. Patent No. 2,161,93 8); trimazosin (U.S. Patent No. 3,669,968); and yohimbine. The disclosures of all such U.S. patents are incorporated herein by reference.

The term "vasodilator" as used herein is meant to include cerebral vasodilators, coronary vasodilators and peripheral vasodilators. Cerebral vasodilators within the scope of this invention include, but are not limited to: bencyclane; cinnarizine; citicoline; cyclandelate (U.S. Patent No. 3,663,597); ciclonicate (German Patent No. 1,910,481); diisopropylamine dichloroacetate (British Patent No. 862,248); eburnamonine (Hermann et al., *Journal of the American Chemical Society*, 1979, 101, 1540); fasudil (U.S. Patent No. 4,678,783); fenoxedil (U.S. Patent No. 3,818,021); flunarizine (U.S. Patent No. 3,773,93 9); ibudilast (U.S. Patent No. 3,850,941); ifenprodil (U.S. Patent No. 3,509,164); lomerizine (U.S. Patent No. 4,663,325); nafronyl (U.S. Patent No. 3,334,096); nicametate (Blicke et al., *Journal of the American Chemical Society*, 1942, 64, 1722); nicergoline; nimodipine (U.S. Patent No. 3,799,934); papaverine (Goldberg, *Chem. Prod. Chem. News*, 1954, 17, 37 1; pentifylline (German Patent No. 860,217); tinofedrine (U.S. Patent No. 3,767,675); vincamine (U.S. Patent No. 3,770,724); vinpocetine (U.S. Patent No. 4,035,750); and viquidil (U.S. Patent No. 2,500,444). The disclosures of all such patents and references are incorporated herein by reference. Coronary vasodilators within the scope of this invention include, but are not limited to: amotriphene (U.S. Patent No. 3,010,965); bendazol (Feitelson, et al., *J. Chem. Soc.* 1958, 2426); benfurodil hemisuccinate (U.S. Patent No. 3,355,463); benziodarone (U.S. Patent No. 3,012,042); chloracizine (British Patent No. 740,932) chromonar (U.S. Patent No. 3,282,93 8); clobenfural (British Patent No. 1,160,925); clonitrate; cloricromen (U.S. Patent No. 4,452,811); dilazep (U.S. Patent No. 3,532,685); dipyridamole (British Patent No. 807,826); droprenilamine

(German Patent No. 2,521,113); efloxate (British Patents Nos. 803,372 and 824,547); erythrityl tetranitrate; etafenone (German Patent No. 1,265,75 8); fendiline (U.S. Patent No. 3,262,977); floredil (German Patent No. 2,020,464); ganglefene (U.S.S.R. Patent No. 115,905); hexestrol bis(P-diethylaminoethyl) ether (Lowe et al. , *J. Chem. Soc.* 1951, 3286); hexobendine (U.S. Patent No. 3,267,103); itramin tosylate (Swedish Patent No. 168,3 08); khellin (Baxter et al., *Journal of the Chemical Society*, 1949, S 30); lidoflazine (U.S. Patent No. 3,267,104); mannitol hexanitrate; medibazine (U.S. Patent No. 3,119,826); nitroglycerin; pentaerythritol tetranitrate; pentrinitrol (German Patent No. 638,422-3); perhexiline; pimefylline (U.S. Patent No. 3,350,400); prenylamine (U.S. Patent No. 3,152,173); propatyl nitrate (French Patent No. 1,103,113); trapidil (East German Patent No. 5 5,956); tricromyl (U.S. Patent No. 2,769,015); trimetazidine (U.S. Patent No. 3,262,852); trolnitrate phosphate; visnadine (U.S. Patents Nos. 2,816,118 and 2,980,699. The disclosures of all such patents and references are incorporated herein by reference. Peripheral vasodilators within the scope of this invention include, but are not limited to: aluminium nicotinate (U.S. Patent No. 2,970,082); bamethan (Corrigan et al., *Journal of the American Chemical Society*, 1945, 67, 1894); bencyclane; betahistine (Walter et al, *Journal of the American Chemical Society*, 1941, 63); bradykinin; brovincamine (U.S. Patent No. 4,146,643); bufeniode (U.S. Patent No. 3,542,870); buflomedil (U.S. Patent No. 3,895,030); butalamine (U.S. Patent No. 3,338,899); cetiedil (French Patent No. 1,460,571); ciclonicate (German Patent No. 1,910,481); cinepazide (Belgium Patent No. 730,345); cinnarizine; cyclandelate; diisopropylamine dichloroacetate; eledoisin (British Patent No. 984,810); fenoxedil; flunarizine; hepronicate (U.S. Patent No. 3,384,642); ifenprodil; iloprost (U.S. Patent No. 4,692,464); inositol niacinate (Badgett et al., *Journal of the American Chemical Society*, 1947, 69, 2907); isoxsuprine (U.S. Patent No. 3.056,836); kallidin (Nicolaides et al., *Biochem. Biophys. Res. Commun.*, 1961, 6, 210); kallikrein (German Patent No. 1,102,973); moxisylyte (German Patent No. 905,738); nafronyl; nicametate; nicergoline; nicofaranose (Swiss Patent No. 366,523); nylidrin (U.S. Patent Nos. 2,661,372 and 2,661,373); pentifylline; pentoxifylline (U.S. Patent No. 3,422,107); piribedil (U.S. Patent No. 3,299,067); prostaglandin El (Merck Index, Twelfth Edition, Budaveri, Ed, New Jersey 1996, page 1353); suloctidil (German Patent No. 2,334,404); tolazoline (U.S. Patent No. 2,161,938); and xanthinol niacinate (German Patent No. 1,102,750). The disclosures of all such patents and references are incorporated herein by reference.

The term "diuretic" as used herein includes but is not limited to diuretic benzothiadiazine derivatives, diuretic organomercurials, diuretic purines, diuretic steroids, diuretic sulfonamide derivatives, diuretic uracils and other diuretics such as amanozine (Austrian Patent No. 168,063); amiloride (Belgium Patent No. 639,386); arbutin (Tschitschibabin et al.,

Annalen, 1930, 479, 303); chlorazanil(Austrian Patent No. 168,063); ethacrynic acid (U.S. Patent No. 3,255,241); etozolin (U.S. Patent No. 3,072,653); hydracarbazine (British Patent No. 856,409); isosorbide (U.S. Patent No. 3,160,641); mannitol; metochalcone (Freudenberg et al., Ber., 1957, 90, 957); muzolimine (U.S. Patent No. 4,018,890); perhexiline; ticrynafen (U.S. Patent No. 3,758,506); triamterene (U.S. Patent No. 3,081,230); and urea. The disclosures of all such patents and references are incorporated herein by reference. Diuretic benzothiadiazine derivatives within the scope of this invention include, but are not limited to: althiazide (British Patent No. 902,658); bendroflumethiazide (U.S. Patent No. 3,392,168); benzthiazide (U.S. Patent No. 3,440,244); benzyl hydrochlorothiazide (U.S. Patent No. 3,108,097); buthiazide (British Patent Nos. 861,367 and 885,078); chlorothiazide (U.S. Patent Nos. 2,809,194 and 2,937,169);chlorthalidone (U.S. Patent No. 3,055,904); cyclopenthiazide (Belgium Patent No. 587,225); cyclothiazide (Whitehead et al *Journal of Organic Chemistry*, 1961, 26, 2814); epithiazide (U.S. Patent No. 3,009,911); ethiazide (British Patent No. 861,367); fenquizone (U.S. Patent No. 3,870,720); indapamide (U.S. Patent No. 3,565,911); hydrochlorothiazide (U.S. Patent No. 3,164,588); hydroflumethiazide (U.S. Patent No. 3,254,076); methyclothiazide (Close et al., *Journal of the American Chemical Society*, 1960, 82, 1132); meticrane (French Patent Nos. M2790 and 1,365,504); metolazone (U.S. Patent No. 3,360,518); paraflutizide (Belgium Patent No. 15 620,829); polythiazide (U.S. Patent No. 3,009,911); quinethazone (U.S. Patent No. 2,976,289); teclothiazide (Close et al., *Journal of the American Chemical Society,* 1960, 82, 1132); and trichlormethiazide (deStevens et al., *Experientia*, 1960, 16, 113). The disclosures of all such patents and references are incorporated herein by reference. Diuretic sulfonamide derivatives within the scope of this invention include, but are not limited to: acetazolamide (U.S. Patent No. 2,554,816); ambuside (U.S. Patent No. 3,188,329); azosemide (U.S. Patent No. 3,665,002); bumetanide (U.S. Patent No, 3,806,534); butazolamide (British Patent No. 769,757); chloraminophenamide (U.S. Patent Nos. 2,909,194; 2,965,655; and 2,965,656); clofenamide (Olivier, *Rec. Trav. Chim.*, 1918, 37, 307); clopamide (U. S. Patent No. 3,459,756); clorexolone (U.S. Patent No. 3,183,243); disulfamide (British Patent No. 851,287); ethozolamide (British Patent No. 795,174); furosemide (U.S. Patent No. 3,058,882); mefruside (U.S. Patent No.3,356,692); methazolamide (U.S. Patent No. 2,783,24 1); piretanide (U.S. Patent No. 4, 010,273); torsemide (U.S. Patent No. 4,018,929); tripamide (Japanese Patent No. 305,585); and xipamide (U.S. Patent No. 3,567,777). The disclosures of all such patents and references are incorporated herein by reference.

Selective neutral endopeptidase inhibitors are taught by Delaney et al. in U.S. Patent Nos. 4,722,810 and 5,223,516 and the use of selective neutral endopeptidase inhibitors alone or in combination with angiotensin converting enzyme inhibitors to treat hypertension are

disclosed by Delaney et al. U.K. Patent Application No. 2,207,351 and by Haslanger et al. in U.S. Patent No. 4,749,688. Compounds possessing both neutral endopeptidase and angiotensin converting enzyme inhibition activity are disclosed by Flynn et al. in U.S. Patent No.5,366,973, European Patent Application No. 481,522 and PCT Patent Applications Nos. WO 93/16103, and 10193, Warshawsky et al. European Patent Applications Nos. 534,363, 534,396 and Fournie- Zaluski European Patent Application No. 524,553, Karanewsky et al. European Patent Application No. 599,444, Karanewsky European Patent Application No. 595, Robl et al., European Patent Application No. 629,627, Robl, U.S. Patent No. 5,362,727 and Patent Application No. 657,453. The disclosures of all such patents and publications incorporated herein by reference.

Further, the anti-hypertensive agents which may be used in accordance with this invention and the pharmaceutically acceptable salts thereof may occur as prodrugs, hydrates or solvates. Said hydrates and solvates are also within the scope of the present invention. Preferred anti-hypertensive agents of the invention include, calcium channel blockers, A-II antagonists, ACE inhibitors and β-blockers. More preferred anti-hypertensive agents of the invention include ACE inhibitors, particularly lisinopril, enalapril and captopril, and A-II antagonists, particularly losartan. The anti-hypertensives described herein are generally commercially available, or they may be made by standard techniques including those described in the references cited above.

The instant compounds are also useful, alone, or in combination with ovulation stimulators such as, but not limited to; bromocriptine (e.g., PARLODEL), luprolide (e.g., LUPRON), clomifene (e.g., CLOMID, SEROPHENE) and pharmaceutically acceptable salts thereof, follicle stimulating hormone (e.g., FERTINEX/ METRODIN, FOLLISTIM, GONAL F), menopausal gonadotropin or mentropins (e.g., REPRONEX), chorionic gonadotropin (e.g., PROFASI, PREGNYL), luteinizing hormone releasing hormone (e.g., GONADORELIN), luteinizing hormone and combinations thereof to treat or prevent ovarian hyper-stimulation syndrome (OHSS). OHSS is a side effect that occurs during infertility treatment with ovulation inducing drugs. OHSS has also been reported to occur as a result of increased endogenous secretion of gonadotropins (*Obstet. Gynecol.* 21:28, 1963; *J. Obstet. Gynaecol. Br. Commonw.* 74:451, 1967). Symptoms of OHSS range from mild to critical and are associated with ovarian enlargement and increased vascular permeability. Women with the most severe symptoms demonstrate increased VEGF levels in follicular fluids that are reversed via the addition of a VEGF antibody indicating that VEGF is responsible for vascular permeabiliy contributing to the pathogenesis of OHSS. Levin, E.R. et al., *J. Clin. Invest.* 102, 1978-1985 (1998). Therefore, a method of treating or preventing ovarian hyper-stimulation syndrome, which comprises

administering a therapeutically effective amount of a claimed compound, alone, or in combination with an ovulation stimulator is within the scope of the present invention.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term "treating cancer" or "treatment of cancer" refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmaceutically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's bloodstream by local bolus injection.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the

dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The scope of the invetion therefore encompasses the use of the instantly claimed compounds in combination with a second compound selected from:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) retinoid receptor modulator,
4) a cytotoxic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor, and
10) another angiogenesis inhibitor.

Preferred angiogenesis inhibitors to be used as the second compound are a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP (matrix metalloprotease) inhibitor, an integrin blocker, interferon-α, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-(chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, or an antibody to VEGF. Preferred estrogen receptor modulators are tamoxifen and raloxifene.

Also included in the scope of the claims is a method of treating cancer which comprises administering a therapeutically effective amount of a claimed compound in combination with radiation therapy and/or in combination with a compound selected from:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) retinoid receptor modulator,
4) a cytotoxic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,

8) an HIV protease inhibitor,

9) a reverse transcriptase inhibitor, and

10) another angiogenesis inhibitor.

And yet another embodiment of the invention is a method of treating cancer which comprises administering a therapeutically effective amount of a compound of Formual I in combination with paclitaxel or trastuzumab.

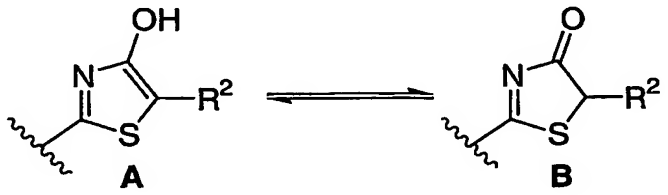
The invention further encompasses a method of treating or preventing cancer which comprises administering a therapeutically effective amount of a claimed compound in combination with a COX-2 inhibitor.

These and other aspects of the invention will be apparent from the teachings contained herein.

Definitions

As used herein, "dual inhibitor" refers to a compound with enzyme $IC_{50} < 1$ μM against both a tyrosine kinase (KDR) and a cyclin-dependent kinase (Cdk4). Dual inhibitor also refers to a compound with cell-based inhibition of both Rb phosphorylation and KDR autophosphorylation of $IC_{50} < 10$ μM. The ratio of dual inhibitory activity is preferably within about 50-fold of each other. Most preferably the ratio is within about 10-fold of each other.

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pp. 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, being included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted. For example, any claim to compound A below is understood to include tautomeric structure B, and vice versa, as well as mixtures thereof.



When any variable occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn

into the ring systems from substituents indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms. If the ring system is polycyclic, it is intended that the bond be attached to any of the suitable carbon atoms on the proximal ring only.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted with one or more substituents" should be taken to be equivalent to the phrase "optionally substituted with at least one substituent" and in such cases the preferred embodiment will have from zero to three substituents.

As used herein, "alkyl" is intended to include both branched, straight-chain, and cyclic saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C_1-C_{10}, as in "C_1-C_{10} alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear or branched, arrangement and may be cyclic or acyclic. For example, "C_1-C_{10} alkyl" specifically includes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on, as well as cyclo-alkyls such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydronaphthalene, methylenecylohexyl, and so on. In some instances, definitions may appear for the same variable reciting both alkyl and cycloalkyl when a different number of carbons is intended for the respective substituents. The use of both terms in one definition should not be interpreted to mean in another definition that "alkyl" does not encompass "cycloalkyl" when only "alkyl" is used.

"Alkoxy" represents an alkyl group of indicated number of carbon atoms as defined above attached through an oxygen bridge.

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, which may be branched or unbranched and cyclic or acyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic carbon-carbon double bonds may be present. Thus, "C_2-C_6 alkenyl" means an alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl, 2-methylbutenyl, cyclohexenyl, methylenylcyclohexenyl, and so on.

The term "alkynyl" refers to a hydrocarbon radical, which may be branched or unbranched and cyclic or acyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Thus, "C_2-C_6

alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups include ethynyl, propynyl, butynyl, 3-methylbutynyl and so on.

In certain instances, substituents may be defined with a range of carbons that includes zero, such as (C_0-C_6)alkylene-aryl. If aryl is taken to be phenyl, this definition would include phenyl itself as well as -CH_2Ph, -CH_2CH_2Ph, -$CH(CH_3)CH_2CH(CH_3)$Ph, and so on.

As used herein, "aryl" is intended to mean phenyl and substituted phenyl, including moieties with a fused benzo group. Examples of such aryl elements include phenyl, naphthyl, tetrahydro-naphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. In cases where the aryl substituent is bicyclic, it is understood that attachment is via the phenyl ring. Unless otherwise indicated, "aryl" includes phenyls substituted with one or more substituents.

The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. As with the definition of heterocycle below, "heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively.

As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo.

The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 5- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, and includes bicyclic groups. "Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, aziridynyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl,

piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl substituent can occur through a carbon atom or via a heteroatom.

R^5 is heterocyclyl. It is understood that attachment of any substituents may occur through a carbon atom or a heteroatom.

The alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl substituents may be substituted or unsubstituted, unless specifically defined otherwise. For example, a $(C_1\text{-}C_6)$alkyl may be substituted with one or more substituents selected from OH, oxo, halogen, alkoxy, dialkylamino, or heterocyclyl, such as morpholinyl, piperidinyl, and so on. In this case, if one substituent is oxo and the other is OH, the following are included in the definition: $-(C{=}O)CH_2CH(OH)CH_3$, $-(C{=}O)OH$, $-CH_2(OH)CH_2CH(O)$, and so on.

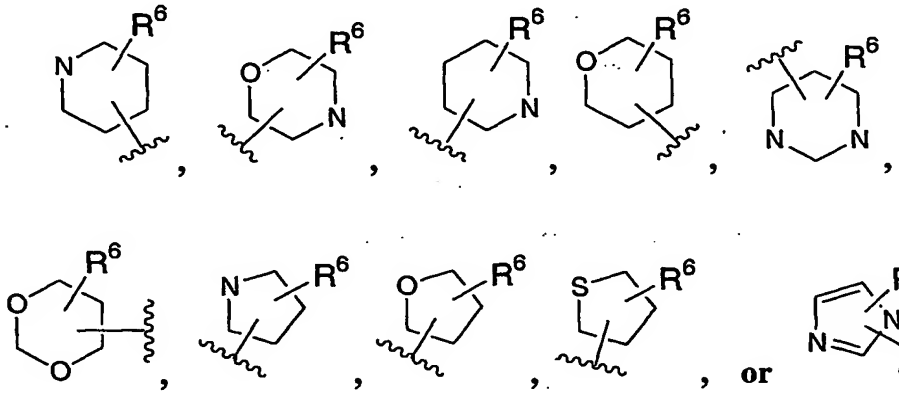
The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed inorganic or organic acids. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like. The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19, hereby incorporated by reference. The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

Preferably R^1 and R^2 are independently H, CN, halogen, OH, phenyl, wherein said phenyl is optionally substituted with one or more substituents selected from R^6, $(C=O)_rO_s(C_1\text{-}C_{10})$alkyl and $(C=O)_rO_s(C_1\text{-}C_{10})$alkyl-$NR^aR^b$.

R^4 is H, CN, halogen, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$perfluoroalkyl.

Most preferably R^1 and R^3 are H, R^2 is CN or phenyl and R^4 is H or $(C_1\text{-}C_6)$alkyl.

Preferably R^5 is:



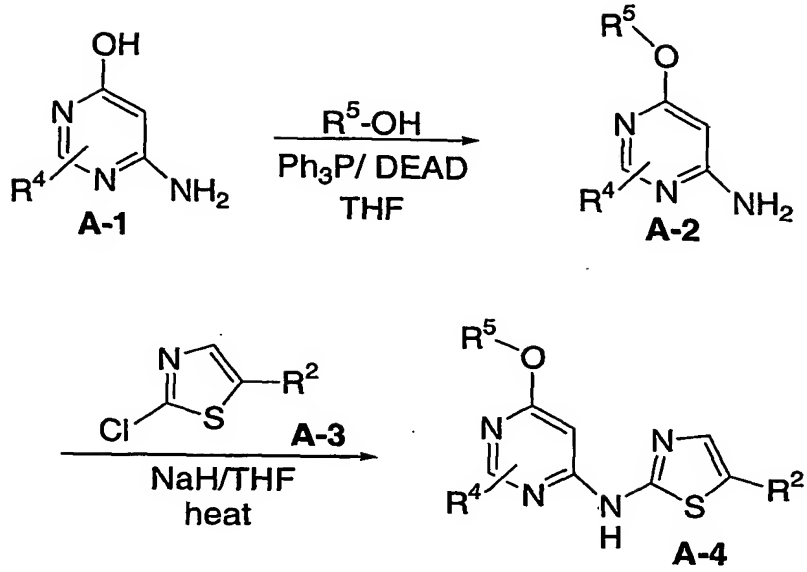
R^5 may be substituted with one or more substituents selected from R^6 and R^6 can be bound to any atom on the ring system

SCHEMES

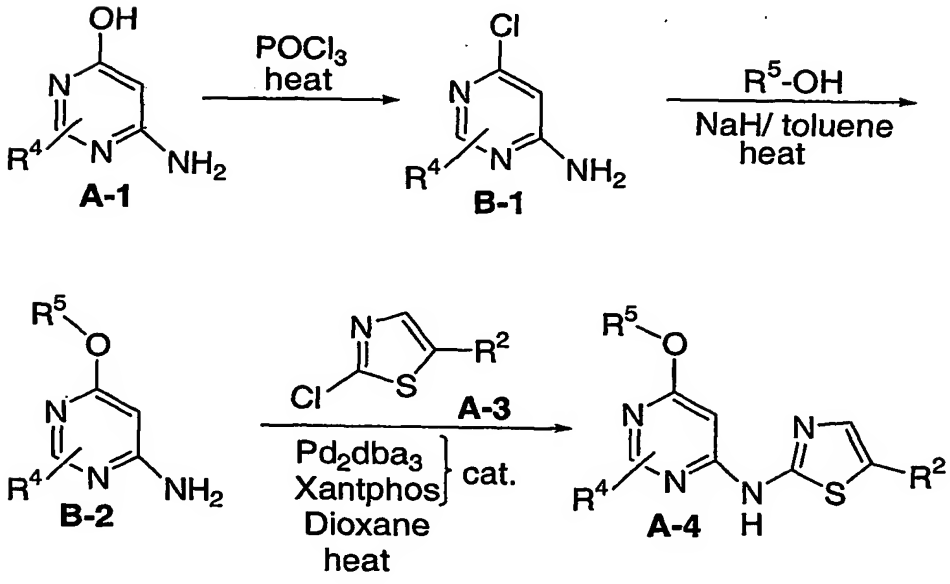
The compounds of this invention may be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. These schemes, therefore, are not limited by the compounds listed or by any particular substituents employed for illustrative purposes. Substituent numbering as shown in the schemes does not necessarily correlate to that used in the claims.

The compounds of the instant invention may be prepared from the general reaction schemes for pyrimidine analogs.

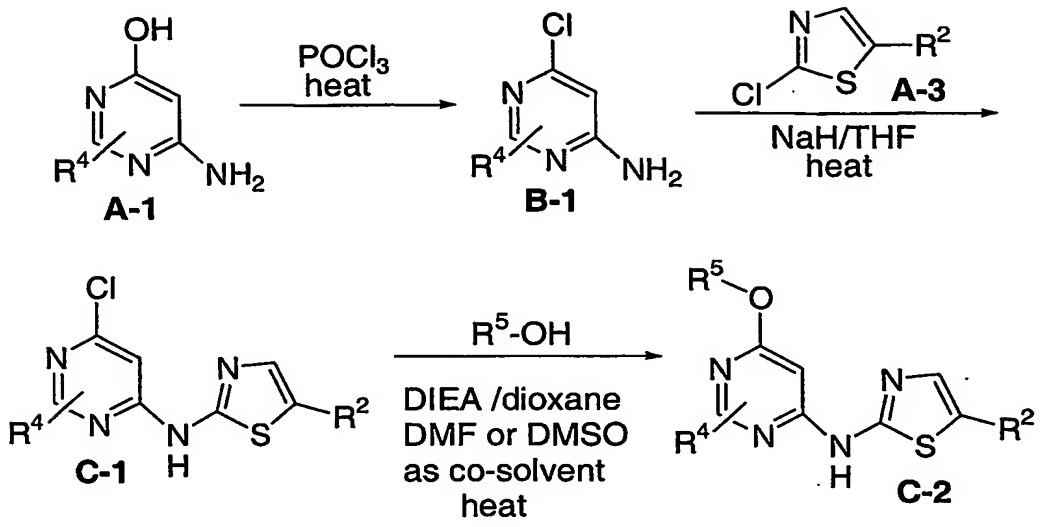
SCHEME A



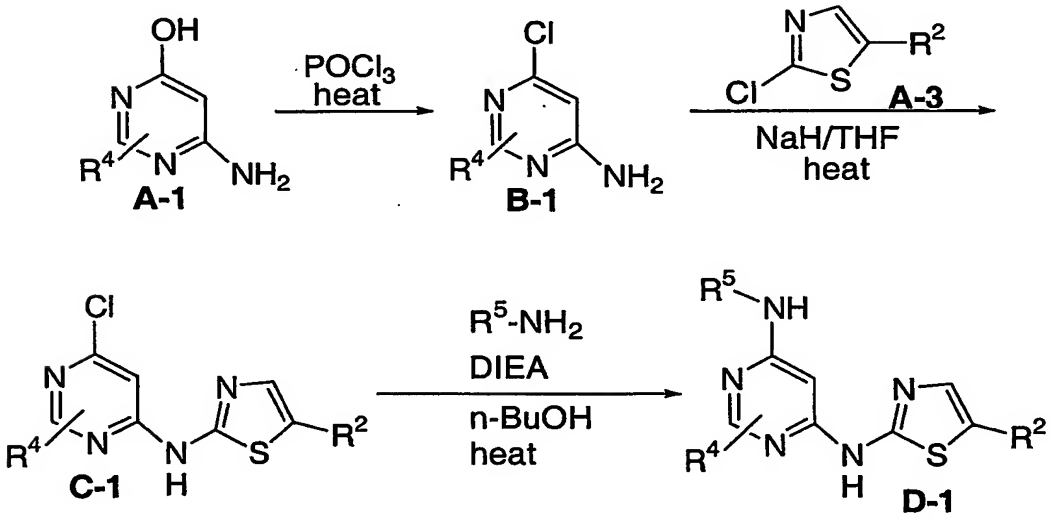
SCHEME B



SCHEME C



SCHEME D



ASSAYS

The compounds of the instant invention described in the Examples were tested by Assays I through IV described below and were found to have kinase inhibitory activity. Compounds disclosed as dual inhibitors showed activity in the Cdk Assay, Assay V. Other assays are known in the literature and could be readily performed by those of skill in the art (see,

for example, Dhanabal et al., *Cancer Res.* 59:189-197; Xin et al., *J. Biol. Chem.* 274:9116-9121; Sheu et al., *Anticancer Res.* 18:4435-4441; Ausprunk et al., *Dev. Biol.* 38:237-248; Gimbrone et al., *J. Natl. Cancer Inst.* 52:413-427; Nicosia et al., *In Vitro* 18:538-549).

I. VEGF RECEPTOR KINASE ASSAY

VEGF receptor kinase activity is measured by incorporation of radio-labeled phosphate into polyglutamic acid, tyrosine, 4:1 (pEY) substrate. The phosphorylated pEY product is trapped onto a filter membrane and the incorporation of radio-labeled phosphate quantified by scintillation counting.

MATERIALS

VEGF Receptor Kinase

The intracellular tyrosine kinase domains of human KDR (Terman, B.I. et al. *Oncogene* (1991) vol. 6, pp. 1677-1683.) and Flt-1 (Shibuya, M. et al. *Oncogene* (1990) vol. 5, pp. 519-524) were cloned as glutathione S-transferase (GST) gene fusion proteins. This was accomplished by cloning the cytoplasmic domain of the KDR kinase as an in frame fusion at the carboxy terminus of the GST gene. Soluble recombinant GST-kinase domain fusion proteins were expressed in Spodoptera frugiperda (Sf21) insect cells (Invitrogen) using a baculovirus expression vector (pAcG2T, Pharmingen).

The other materials used and their compositions were as follows:

Lysis buffer: 50 mM Tris pH 7.4, 0.5 M NaCl, 5 mM DTT, 1 mM EDTA, 0.5% triton X-100, 10% glycerol, 10 μg/mL of each leupeptin, pepstatin and aprotinin and 1 mM phenylmethylsulfonyl fluoride (all Sigma).

Wash buffer: 50 mM Tris pH 7.4, 0.5 M NaCl, 5 mM DTT, 1 mM EDTA, 0.05% triton X-100, 10% glycerol, 10 μg/mL of each leupeptin, pepstatin and aprotinin and 1 mM phenylmethylsulfonyl fluoride.

Dialysis buffer: 50 mM Tris pH 7.4, 0.5 M NaCl, 5 mM DTT, 1 mM EDTA, 0.05% triton X-100, 50% glycerol, 10 μg/mL of each leupeptin, pepstatin and aprotinin and 1 mM phenylmethylsulfonyl fluoride.

10 X reaction buffer: 200 mM Tris, pH 7.4, 1.0 M NaCl, 50 mM $MnCl_2$, 10 mM DTT and 5 mg/mL bovine serum albumin (Sigma).

Enzyme dilution buffer: 50 mM Tris, pH 7.4, 0.1 M NaCl, 1 mM DTT, 10% glycerol, 100 mg/mL BSA.

10 X Substrate: 750 μg/mL poly (glutamic acid, tyrosine; 4:1) (Sigma).

Stop solution: 30% trichloroacetic acid, 0.2 M sodium pyrophosphate (both Fisher).

Wash solution: 15% trichloroacetic acid, 0.2 M sodium pyrophosphate.

Filter plates: Millipore #MAFC NOB, GF/C glass fiber 96 well plate.

METHOD

A. Protein purification

1. Sf21 cells were infected with recombinant virus at a multiplicity of infection of 5 virus particles/ cell and grown at 27°C for 48 hours.

2. All steps were performed at 4°C. Infected cells were harvested by centrifugation at 1000 X g and lysed at 4°C for 30 minutes with 1/10 volume of lysis buffer followed by centrifugation at 100,000Xg for 1 hour. The supernatant was then passed over a glutathione Sepharose column (Pharmacia) equilibrated in lysis buffer and washed with 5 volumes of the same buffer followed by 5 volumes of wash buffer. Recombinant GST-KDR protein was eluted with wash buffer/10 mM reduced glutathione (Sigma) and dialyzed against dialysis buffer.

B. VEGF receptor kinase assay

1. Add 5 μL of inhibitor or control to the assay in 50% DMSO.
2. Add 35 μL of reaction mix containing 5 μL of 10 X reaction buffer, 5 μL 25 mM ATP/10 μCi [^{33}P]ATP (Amersham), and 5 μL 10 X substrate.
3. Start the reaction by the addition of 10 μL of KDR (25 nM) in enzyme dilution buffer.
4. Mix and incubate at room temperature for 15 minutes.
5. Stop by the addition of 50 μL stop solution.
6. Incubate for 15 minutes at 4°C.
7. Transfer a 90 μL aliquot to filter plate.
8. Aspirate and wash 3 times with wash solution.

9. Add 30 μL of scintillation cocktail, seal plate and count in a Wallac Microbeta scintillation counter.

II HUMAN UMBILICAL VEIN ENDOTHELIAL CELL MITOGENESIS ASSAY

Human umbilical vein endothelial cells (HUVECs) in culture proliferate in ...e to VEGF treatment and can be used as an assay system to quantify the effects of KDR ...se inhibitors on VEGF stimulation. In the assay described, quiescent HUVEC monolayers ...ted with vehicle or test compound 2 hours prior to addition of VEGF or basic fibroblast ... factor (bFGF). The mitogenic response to VEGF or bFGF is determined by measuring ...rporation of [^{3}H] thymidine into cellular DNA.

MATERIALS

HUVECs: HUVECs frozen as primary culture isolates are obtained from Clonetics Corp. Cells are maintained in Endothelial Growth Medium (EGM; Clonetics) and are used for mitogenic assays described in passages 1-5 below.

Culture Plates: NUNCLON 96-well polystyrene tissue culture plates (NUNC #167008).

Assay Medium: Dulbecco's modification of Eagle's medium containing 1 mg/mL glucose (low-glucose DMEM; Mediatech) plus 10% (v/v) fetal bovine serum (Clonetics).

Test Compounds: Working stocks of test compounds are diluted serially in 100% dimethylsulfoxide (DMSO) to 400-fold greater than their desired final concentrations. Final dilutions to 1X concentration are made directly into Assay Medium immediately prior to addition to cells.

10X Growth Factors: Solutions of human $VEGF_{165}$ (500 ng/mL; R&D Systems) and bFGF (10 ng/mL; R&D Systems) are prepared in Assay Medium.

10X [^{3}H]Thymidine: [Methyl-^{3}H]thymidine (20 Ci/mmol; Dupont-NEN) is diluted to 80 μCi/mL in low-glucose DMEM.

Cell Wash Medium: Hank's balanced salt solution (Mediatech) containing 1 mg/mL bovine serum albumin (Boehringer-Mannheim).

Cell Lysis Solution: 1 N NaOH, 2% (w/v) Na_2CO_3.

METHOD

1. HUVEC monolayers maintained in EGM are harvested by trypsinization and plated at a density of 4000 cells per 100 µL Assay Medium per well in 96-well plates. Cells are growth-arrested for 24 hours at 37°C in a humidified atmosphere containing 5% CO_2.

2. Growth-arrest medium is replaced by 100 µL Assay Medium containing either vehicle (0.25% [v/v] DMSO) or the desired final concentration of test compound. All determinations are performed in triplicate. Cells are then incubated at 37°C with 5% CO_2 for 2 hours to allow test compounds to enter cells.

3. After the 2-hour pretreatment period, cells are stimulated by addition of 10 µL/well of either Assay Medium, 10X VEGF solution or 10X bFGF solution. Cells are then incubated at 37°C and 5% CO_2.

4. After 24 hours in the presence of growth factors, 10X [^{3}H] thymidine (10 µL/well) is added.

5. Three days after addition of [^{3}H]thymidine, medium is removed by aspiration, and cells are washed twice with Cell Wash Medium (400 µL/well followed by 200 µL/well). The washed, adherent cells are then solubilized by addition of Cell Lysis Solution (100 µL/well) and warming to 37°C for 30 minutes. Cell lysates are transferred to 7-mL glass scintillation vials containing 150 µL of water. Scintillation cocktail (5 mL/vial) is added, and cell-associated radioactivity is determined by liquid scintillation spectroscopy.

Based upon the foregoing assays the compounds of the present invention are inhibitors of VEGF and thus are useful for the inhibition of angiogenesis, such as in the treatment of ocular disease, e.g., diabetic retinopathy and in the treatment of cancers, e.g., solid tumors. The instant compounds inhibit VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC_{50} values between 0.01 - 5.0 µM. These compounds may also show selectivity over related tyrosine kinases (e.g., FGFR1 and the Src family; for relationship between Src kinases and VEGFR kinases, see Eliceiri et al., *Molecular Cell*, Vol. 4, pp.915-924, December 1999).

III. FLT-1 KINASE ASSAY

Flt-1 was expressed as a GST fusion to the Flt-1 kinase domain and was expressed in baculovirus/insect cells. The following protocol was employed to assay compounds for Flt-1 kinase inhibitory activity:

1. Inhibitors were diluted to account for the final dilution in the assay, 1:20.
2. The appropriate amount of reaction mix was prepared at room temperature:
   10X Buffer (20 mM Tris pH 7.4/0.1 M NaCl/1 mM DTT final)
   0.1M $MnCl_2$ (5 mM final)
   pEY substrate (75 µg/mL)
   ATP/[^{33}P]ATP (2.5 µM/1 µCi final)
   BSA (500 µg/mL final).
3. 5 µL of the diluted inhibitor was added to the reaction mix. (Final volume of 5 µL in 50% DMSO). To the positive control wells, blank DMSO (50%) was added.
4. 35 µL of the reaction mix was added to each well of a 96 well plate.
5. Enzyme was diluted into enzyme dilution buffer (kept at 4°C).
6. 10 µL of the diluted enzyme was added to each well and mix (5 nM final). To the negative control wells, 10 µL 0.5 M EDTA was added per well instead (final 100 mM).
7. Incubation was then carried out at room temperature for 30 minutes.
8. Stopped by the addition of an equal volume (50 µL) of 30% TCA/0.1M Na pyrophosphate.
9. Incubation was then carried out for 15 minutes to allow precipitation.
10. Transfered to Millipore filter plate.
11. Washed 3X with 15% TCA/0.1M Na pyrophosphate (125 µL per wash).
12. Allowed to dry under vacuum for 2-3 minutes.
13. Dryed in hood for ~ 20 minutes.
14. Assembled Wallac Millipore adapter and added 50 µL of scintillant to each well and counted.

IV. FLT-3 KINASE ASSAY

Flt-3 was expressed as a GST fusion to the Flt-3 kinase domain, and was expressed in baculovirus/insect cells. The following protocol was employed to assay compounds for Flt-3 kinase inhibitory activity:

1. Dilute inhibitors (account for the final dilution into the assay, 1:20)
2. Prepare the appropriate amount of reaction mix at room temperature.
   10X Buffer (20 mM Tris pH 7.4/0.1 M NaCl/1 mM DTT final)
   0.1M $MnCl_2$ (5 mM final)
   pEY substrate (75 µg/mL)

ATP/[^{33}P]ATP (0.5 μM/L μCi final)
BSA (500 μg/mL final)

3. Add 5 μL of the diluted inhibitor to the reaction mix. (Final volume of 5 μL in 50% DMSO). Positive control wells - add blank DMSO (50%).
4. Add 35 μL of the reaction mix to each well of a 96 well plate.
5. Dilute enzyme into enzyme dilution buffer (keep at 4°C).
6. Add 10 μL of the diluted enzyme to each well and mix (5-10 nM final). Negative control wells – add 10 μL 0.5 M EDTA per well instead (final 100 mM)
7. Incubate at room temperature for 60 minutes.
8. Stop by the addition of an equal volume (50 μL) of 30% TCA/0.1M Na pyrophosphate.
9. Incubate for 15 minutes to allow precipitation.
10. Transfer to Millipore filter plate.
11. Wash 3X with 15% TCA/0.1M Na pyrophosphate (125 μL per wash).
12. Allow to dry under vacuum for 2-3 minutes.
13. Dry in hood for ~ 20 minutes.
14. Assemble Wallac Millipore adapter and add 50 μL of scintillant to each well and count.

V. CYCLIN DEPENDENT KINASE ASSAYS

CDK4 ASSAY

Human cyclin D2-glutathione-S-transferase fused Cdk4 (GST-Cdk4) complexes were produced in Sf9 cells that had been co-infected with recombinant baculoviruses encoding cDNAs for cyclin D2 and GST-Cdk4. Cyclin D2-GST-Cdk4 complex was absorbed to glutathione-sepharose 4B (Pharmacia Biotech) and eluted by digestion by precision protease. Active cyclin D2-Cdk4 complexes were further purified by HPLC on Mono Q.

Cyclin D2-Cdk4 assays for determinations of the IC_{50} values were performed in 96 well P81-paper filter plates (Millipore).

1. Purified cyclin D2-Cdk4 was incubated with 50 μM ATP, 1 μCi [^{33}P]ATP and 100 μM G1 peptide (RPPTLSPIPHIPR) in R buffer (20 μL of reaction buffer containing 20 mM Tris-HCl pH 7.4, 10 mM $MgCl_2$, 4.5 mM 2-mercaptoethanol and 1 mM EGTA) for 45 minutes at 30°C. G1 peptide is identical to 775-787 amino acid residues of human retinoblastoma protein (pRb) and Ser site of pRb is specifically phosphorylated by Cdk4 (Kitagawa, M. et al, *EMBO Journal*, vol. 15, pp. 7060-7069, 1996).
2. Reaction was stopped by adding 10 μL of 350 mM H_3PO_4.

3. Peptides were trapped on the 96 well filter plate and filters were washed with 75 mM H_3PO_4.

4. Radioactivity was determined by TOP count (Packard).

CDK2 ASSAY

Human cyclin A-Cdk2 complexes were produced in Sf9 cells that had been co-infected with recombinant baculoviruses encoding cDNAs for cyclin A and Cdk2. Active cyclin A-Cdk2 complexes were purified by HPLC on Mono Q, Hydroxyapatite and Mono S.

Cyclin A-Cdk2 assays for determinations of the IC_{50} values were performed according to the same method as cyclin D2-Cdk4 assay above.

1. Purified cyclin A-Cdk2 was incubated with 50 μM ATP, 0.5 μCi [^{33}P]ATP and 0.01 mg/mL of S1 peptide (AKAKKTPKKAKK) in R buffer for 45 minutes at 30°C. S1 peptide includes amino acid residues of human histone H1 (Kitagawa, M. et al, *EMBO Journal*, vol. 15, pp. 7060-7069, 1996).

2. Reaction was stopped by adding 10 μL of 350 mM H_3PO_4.

3. Peptides were trapped on the 96 well filter plate and filters were washed with 75 mM H_3PO_4.

4. Radioactivity was determined by TOP count (Packard).

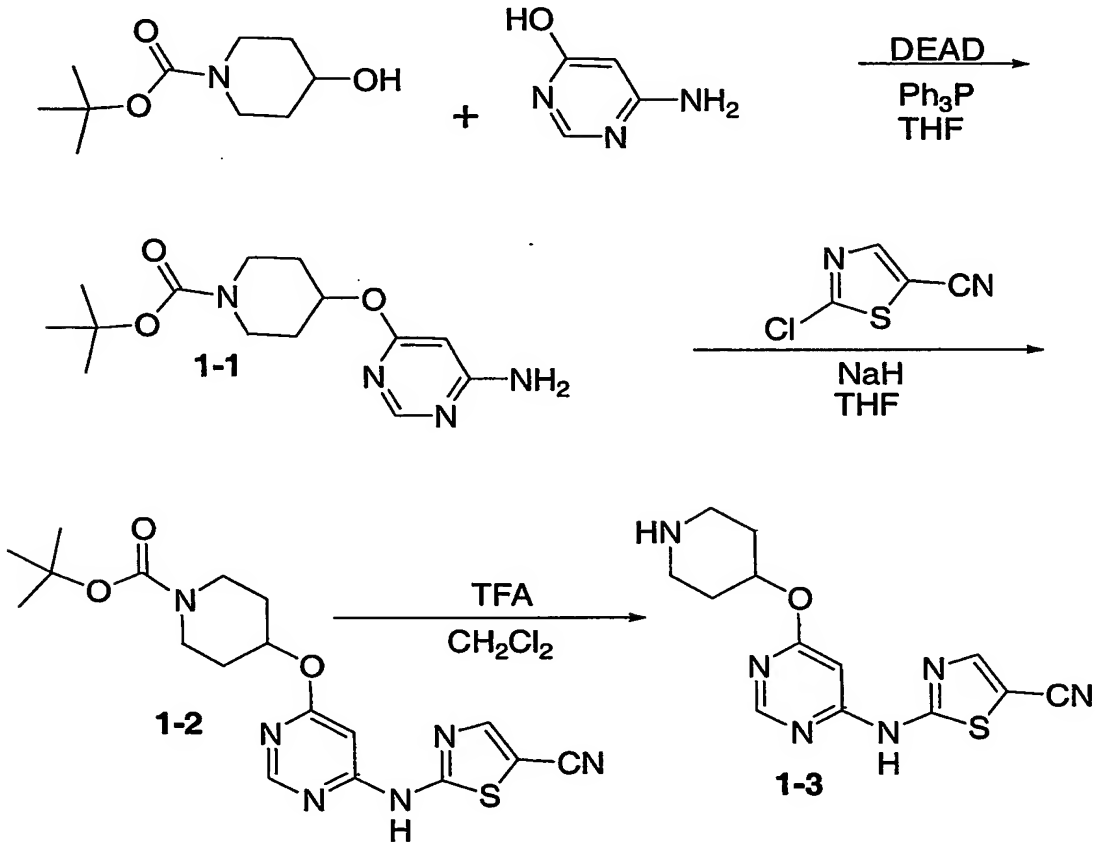
EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limiting of the reasonable scope thereof.

Some of the specific compounds exemplified herein are the protonated salts of amine compounds. The term "free form" refers to the amine compounds in non-salt form. The encompassed pharmaceutically acceptable salts not only include the salts exemplified for the specific compounds described herein, but also all the typical pharmaceutically acceptable salts of the free form of compounds of Formula I. The free form of the specific salt compounds described may be isolated using techniques known in the art. For example, the free form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free form may differ from their respective salt forms in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free forms for purposes of the invention.

All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

SCHEME 1



Synthesis of tert-butyl-4-[(6-aminopyrimidin-4-yl)oxy]piperidine-1-carboxylate (1-1)

4-Hydroxy-6-aminopyrimidine (554 mg, 5 mmol) was added to a solution tert-butyl-4-hydroxy-piperidine-1-carboxylate (1.21 gm, 6 mmol) and triphenylphosphine (1.83 gm, 7 mmol) in dry THF (40 mL). This mixture was cooled in an ice bath and diethyldiazodicarboxlate (DEAD) (1.15 mL, 7 mmol) was added dropwise. The reaction was stirred at ice bath temperature for one hour and then gradually warmed to room temperature over two more hours. The solvent was removed under vacuum and the residue was chromatograghed on silica gel eluting with a 50-100% ethyl acetate/hexane gradient. The semipurified product was rechromatograhed on silica gel eluting with a 1-3% methanol/chloroform gradient. This material was triturated with diethyl ether to give the title compound as a white crystalline solid, mp: 168-

174°C. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.26 (1H,s), 5.80 (1H,s), 5.24 (1H,m), 5.08 (2H, m), 3.76 (2H,m), 3.27 (2H,m), 1.96 (2H,m), 1.71 (2H, m), 1.48(9H, s). M+1 = 295.3

Synthesis of tert-butyl-4-({6-[(5-cyano-1,3-thiazol-2-yl)amino]pyrimidin-4-yl}oxy) piperidine-1-carboxylate (1-2)

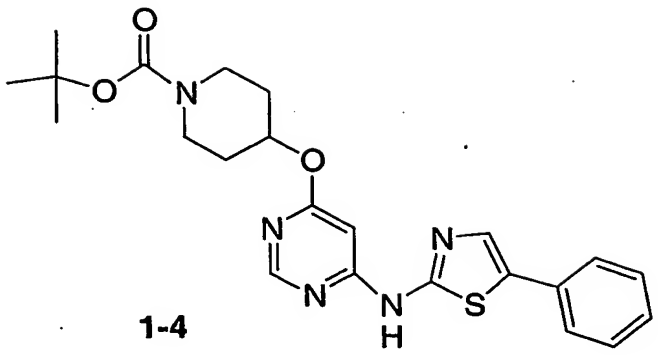
Sodium hydride (60% in mineral oil, 95 mg, 2.4 mmol) was added to a solution of tert-butyl-4-[(6-aminopyrimidin-4-yl)oxy]piperidine-1-carboxylate (295 mg, 1 mmol) in dry THF (4 mL). After gas evolution ceased (~1/4 hr) a solution of 2-chloro-1,3-thiazole-5-carbonitrile (160 mg, 1.1 mmol) dissolved in THF (2 mL) was added and the reaction was warmed to ~50°C overnight (~ 8 hours. The cooled reaction was diluted with ethyl acetate and 2N HCl (0.7 mL) was added, followed by saturated $NaHCO_3$ solution. The ethyl acetate exact was dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was chromatographed on silica gel eluting with a 0-2% methanol/chloroform gradient. The appropriate fractions were combined and the solvents removed. The resultant residue was triturated with diethyl ether to give the title compound as a white solid, mp: 224-227°C. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.63(1H,s), 7.95(1H,s), 7.27(1H,s), 6.70(1H,br s), 5.36 (1H,m), 3.77(2H,m), 3.30 (2H,m), 2.05 (2H,m), 1.75 (2H,m), 1.48 (9H,s). M+1 = 403.2

Synthesis of 2-{[6-(piperidin-4-yloxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile (1-3)

A solution of tert-butyl-4-({6-[(5-cyano-1,3-thiazol-2-yl)amino] pyrimidin-4-yl}oxy)piperidine-1-carboxylate (56 mg, 0.14 mmol) in methylene chloride (5 mL) containing TFA (0.5 mL) was stirred at room temperature over night. The solvents were evaporated and the residue was chased with chloroform (2X). The residue was dissolved in methanol, filtered through a plug of charcoal and the solvent nearly all removed under vacuum. This residue was triturated with ethyl acetate to give the title compound as a crystalline TFA salt, mp: 240-242°C. ^{1}H-NMR (500 MHz, DMSO-d_6): 8.68(1H,s), 8.33(1H,s), 6.41(1H,s), 5.33(1H,m), 3.26(2H,m), 3.13 (2H,m), 2.11(2H,m), 1.86(2H,m). M+1 = 303.2

Compounds **1-4** through **1-9** were synthesized via the same protocol shown in Scheme 1 by using an appropriate alcohol and 5-substituted 2-chlorothiazole.

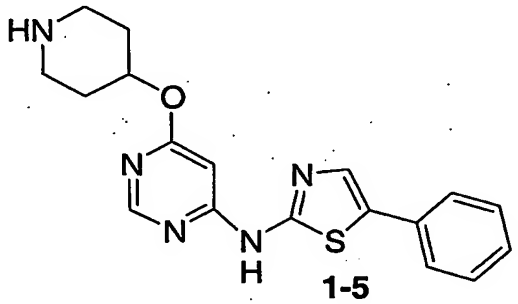
Synthesis of tert-butyl-4-({6-[(5-phenyl-1,3-thiazol-2-yl)amino]pyrimidin-4-yl}oxy) piperidine-1-carboxylate (1-4)



1-4

The title compound was prepared according to the protocol described in Scheme 1 except 2-chloro-5-phenyl-1,3-thiazole was substituted for 2-chloro-1,3-thiazole-5-carbonitrile. The product was obtained as a white solid, mp: 234-235°C.
^{1}H-NMR (500MHz, $CDCl_3$): 8.60 (1H,s), 7.55 (3H, m), 7.46 (2H,t, J=8hz), 7.38 (1H, t, J=7Hz), 6.47 (1H,s), 5.31 (1H,m), 3.75 (2H,m), 3.30 (2H,m), 1.98 (2H,m), 1.75 (2H,m), 1.48 (9H,s). M+1 = 454.2

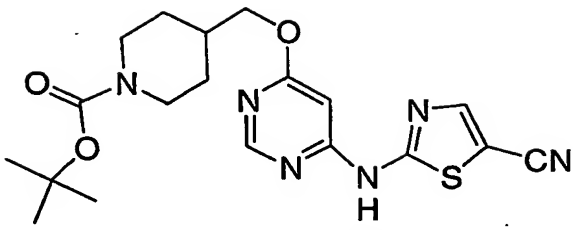
Synthesis of N-(5-phenyl-1,3-thiazol-2-yl)-6-(piperidin-4-yloxy)pyrimidin-4-amine (1-5)



1-5

The title compound was prepared according to the procedure described in Scheme 1 using compound **1-4**. This product was obtained as the TFA salt, mp: 241-243°C. ^{1}H-NMR (500 MHz, DMSO-d_6): 8.61(1H,s), 8.51 (1H,br s), 8.43(1H, br s), 7.84 (1H,s), 7.60 (2H, d, J=8Hz), 7.41(2H, t, J=8 Hz), 7.29 (1H, t, J=7.1Hz), 6.43 (1H, br s), 5.31 (1H,m), 3.27 (2H, m), 3.14 (2H,m), 2.13 (2H,m), 1.89 (2H,m). M+1= 354.2

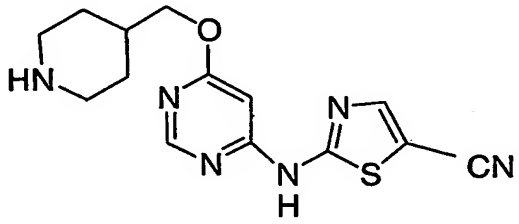
Synthesis of tert-butyl-4-[({6-[(5-cyano-1,3-thiazol-2-yl)amino]pyrimidin-4-yl}oxy) methyl]-piperidine-1-carboxylate (1-6)



1-6

The title compound was prepared according to the procedure described in Scheme 1 except tert-butyl-4-(hydroxymethyl)piperidine-1-carboxylate was substituted for tert-butyl-4-hydroxy-piperidine-1-carboxylate. The product was obtained as a white crystalline solid, mp: 228-229°C. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.63 (1H,s), 7.95 (1H,s), 7.25 (1H,s), 6.60 (1S, br s), 4.28(2H,d, J=6.4 Hz), 4.16 (2H, d, J=13.4 Hz), 2.74 (2H, t, J=12Hz), 1.79 (2H, d, J= 11.5 Hz), 1.46 (9H,s), 1.26 (2H,m). M+1 = 417.2

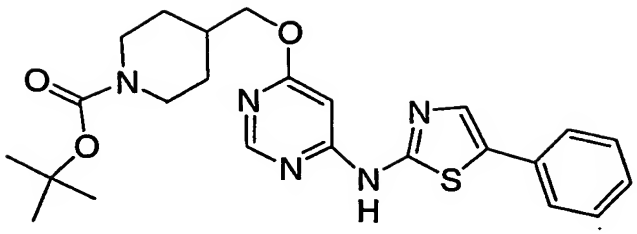
2-{[6-(piperidin-4-ylmethoxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile (1-7)



1-7

The title compound was prepared according to the procedure described in Scheme 1 using compound **1-6** above. This product was obtained as the TFA salt, mp: 244-245°C. ^{1}H-NMR (500 MHz, DMSO-d_6): 8.67(1H,s), 8.53(1H,br s), 8.32 (1H, s), 8.21(1H, br s), 6.40 (1H,s), 4.21 (2H, d, J=6.1Hz), 3.31 (2H, br d, J=13 Hz), 2.89 (2H, m), 2.07 (1H, m), 1.88 (2H, d, J=12.5Hz),1.45 (2H, q, J=12.5 Hz). M+1 = 317.2

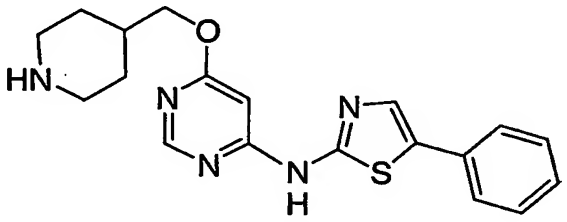
tert-butyl-4-[({6-[(5-phenyl-1,3-thiazol-2-yl)amino]pyrimidin-4-yl}oxy)methyl]-piperidine-1-carboxylate (1-8)



1-8

The title compound was prepared according to the procedure described in Scheme 1 except tert-butyl-4-(hydroxymethyl)piperidine-1-carboxylate was substituted for tert-butyl-4-hydroxy-piperidine-1-carboxylate and 2-chloro-5-phenyl-1,3-thiazole was substituted for 2-chloro-1,3-thiazole-5-carbonitrile, mp: 222-223°C.
^{1}H-NMR (500MHz, $CDCl_3$): 8.65 (1H,s), 7.45-7.55 (5H, m), 7.25 (1H,s), 6.61 (1H,s), 4.24(2H, d, J=6.6 Hz), 4.16 (2H,m), 2.74 (2H,br t, J=11Hz), 1.97 (1H,m), 1.78 (2H,d, J=13Hz), 1.47 (9H,s), 1.25 (2H, br m). M+1 = 468.2

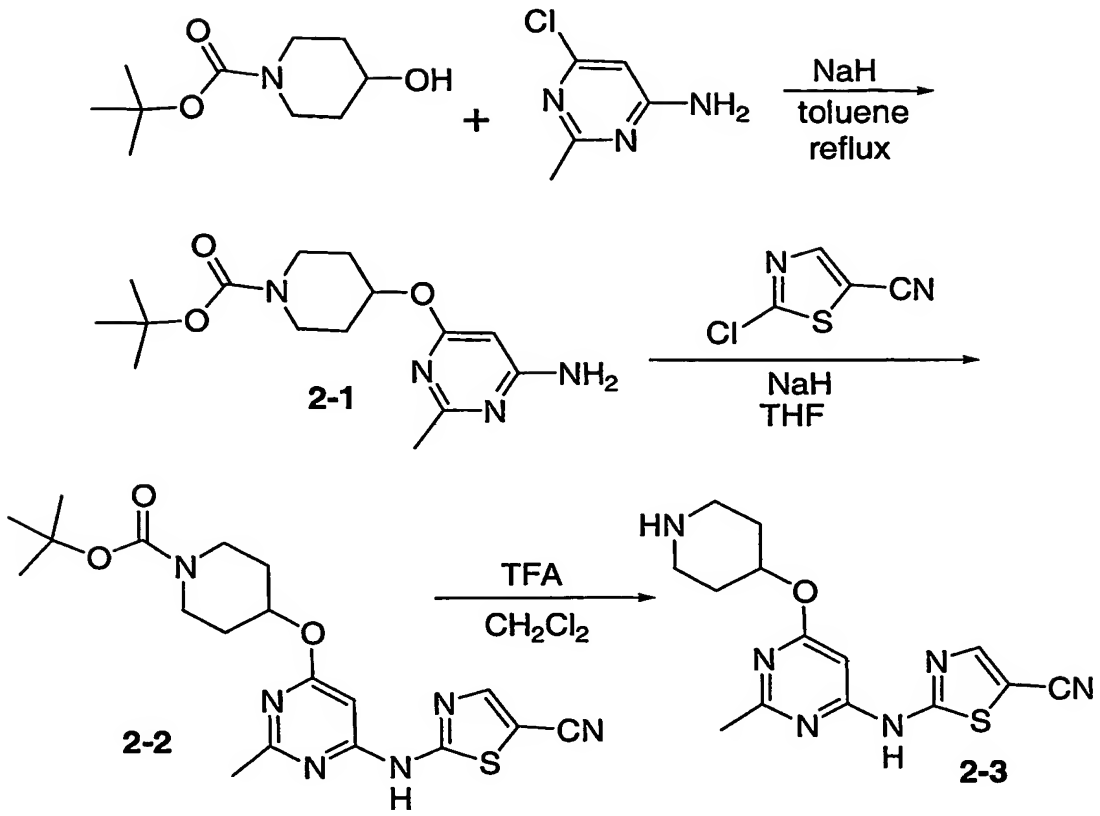
N-(5-phenyl-1,3-thiazol-2-yl)-6-(piperidin-4-ylmethoxy)pyrimidin-4-amine (**1-9**)



1-9

The title compound was prepared according to the procedure described in Scheme 1 using compound **1-8** above. This product was obtained as the TFA salt, mp: 238-239°C. ^{1}H-NMR (500 MHz, DMSO-d_6): 8.60(1H,s), 8.53(1H,br s), 8.19 (1H, br s), 7.84(1H, s), 7.61(2H,d, J=7.3Hz), 7.43(2H, t, J=7.8Hz), 7.29(1H, t, J=7.3Hz), 6.43 (1H,s), 4.23 (2H, d, J=6.4Hz), 3.31 (2H, br d, J=12 Hz), 2.92 (2H, q, J=10.5Hz), 2.17 (1H, m), 1.88 (2H, d, J=14Hz),1.45 (2H,q, J=10Hz). M+1 = 368.2

SCHEME 2



Synthesis of tert-butyl-4-[(6-amino-2-methylpyrimidin-4-yl)oxylpiperidine-1-carboxylate (2-1)

Solid 6-chloro-2-methylpyrimidin-4-amine (720 mg, 5 mmol), which is prepared from 6-amino-2-methylpyrimidin-4-ol as described in *Chem. Ber.*, 75, 755(1942), was added to a solution of tert-butyl-4-hydroxy-piperidine-1-carboxylate (1.05 gm, 5.2 mmol) in dry toluene containing sodium hydride (60% in mineral oil, 238 mg, ~6 mmol). The reaction mixture was heated at reflux for 18 hours. The cooled reaction was diluted with ethyl acetate, washed with saturated $NaHCO_3$ and the solution was dried over anhydrous Na_2SO_4, filtered and the solvents evaporated. The residue was purified by chromatography on silica gel eluting with a 40-70% ethyl acetate/hexane gradient. The appropriate fractions were combined, the solvent evaporated, and the residue triturated with diethyl ether to give the title compound as a white crystalline solid, mp: 142-145°C. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.59 (1H,s), 5.21 (1H,m), 4.81 (2H, br s), 3.72 (2H,m), 3.28 (2H,m), 2.43 (3H,s), 1.93 (2H,m), 1.68 (2H,m), 1.46 (9H,s). M+1 = 309.2

Synthesis of tert-butyl-4-({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}oxy)piperidine-1-carboxylate (2-2)

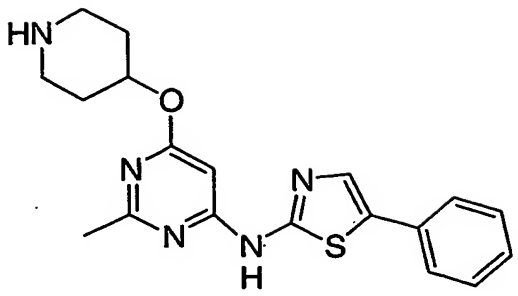
Sodium hydride (60% in mineral oil, 121 mg, 3 mmol) was added to a solution of tert-butyl-4-[(6-amino-2-methylpyrimidin-4-yl)oxy]piperidine-1-carboxylate (360 mg, 1.17 mmol) in dry THF (5 mL). After gas evolution ceased (~1/4 hr) a solution of 2-chloro-1,3-thiazole-5-carbonitrile (189 mg, 1.3 mmol) dissolved in THF (2 mL) was added and the reaction was warmed to ~50°C for 22 hours. The reaction progress was monitored by LC/MS periodically adding additional sodium hydride (another 180 mg) and 2-chloro-1,3-thiazole-5-carbonitrile (another 286 mg) in portions until the reaction was complete. The cooled reaction was diluted with ethyl acetate and 2N HCl (3 mL) was added, followed by saturated $NaHCO_3$ solution. The ethyl acetate extract was dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was purified by chromatography on silica gel eluting with a 15-40% ethyl acetate/hexane gradient. The appropriate fractions were combined and the solvents removed. The resultant residue was triturated with diethyl ether to give the title compound as a white solid, mp: 227-228°C. ^{1}H-NMR (500 MHz, $CDCl_3$): 9.90(1H, br s), 5.97 (1H,s), 5.34(1H,m), 3.78(2H,m), 3.29(2H,m), 2.62 (3H,s), 1.96(2H,m), 1.72(2H,m), 1.48(9H,s). M+1 = 417.2

Synthesis of 2-{[2-methyl-6-(piperidin-4-yloxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile (**2-3**)

A solution of tert-butyl-4-({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}oxy)piperidine-1-carboxylate (126 mg, 0.30 mmol) in chloroform (5 mL) containing TFA (0.75 mL) was stirred at room temperature over night. The solvents were evaporated and the residue was chased with chloroform (2X). The residue was dissolved in a minimum amount of methanol and diluted with diethyl ether and the title compound crystallized out as the TFA salt, mp: >250°C. ^{1}H-NMR (500 MHz, DMSO-d_6): 8.45(2H, br s), 8.32(1H,s), 622(1H,s), 5.32(1H,m), 3.26(2H,m), 3.14 (2H,m), 2.56(3H, s), 2.11(2H,m), 1.85(2H,m). M+1 = 317.2

Compounds **2-4** through **2-7** below were synthesized via the same protocol shown in Scheme 2 by using the appropriate alcohol and 5-substituted 2-chlorothiazole.

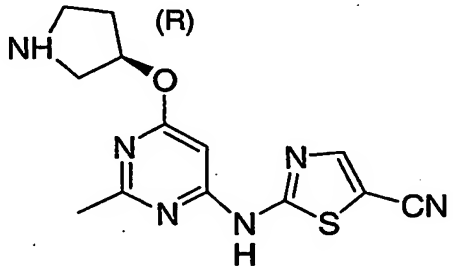
Synthesis of N-(5-phenyl-1,3-thiazol-2-yl)-6-(piperidin-4-yloxy)-2-methylpyrimidin-4-amine (**2-4**)



2-4

The title compound was prepared according to the procedure described in Scheme 2 substituting 2-chloro-5-phenyl-1,3-thiazole for 2-chloro-1,3-thiazole-5-carbonitrile. This product was obtained as the TFA salt, mp: 247-249°C. ^{1}H-NMR (500 MHz, DMSO-d6): 8.52(1H,br s), 8.45(1H,br s), 7.82 (1H,s), 7.61 (2H, d, J=7.3Hz), 7.41(2H, t, J=7.6 Hz), 7.29 (1H, t, J=7.6Hz), 6.24 (1H, s), 5.31 (1H,m), 3.25 (2H, m), 3.15 (2H,m), 2.54(3H,s), 2.11 (2H,m), 1.87 (2H,m). M+1= 368.2

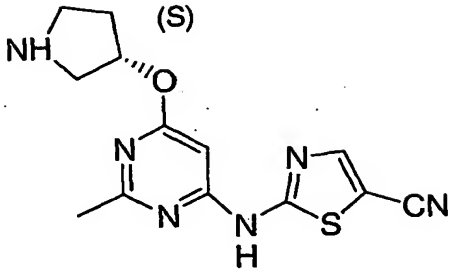
Synthesis of 2-({2-methyl-6-[(3R)-pyrrolidin-3-yloxy]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile (2-5)



2-5

The title compound was prepared according to the procedure described in Scheme 2 except tert-butyl-(3R)-3-hydroxypyrrolidine-1-carboxylate was substituted for tert-butyl-4-hydroxy-piperidine-1-carboxylate. This product was obtained as the TFA salt, mp: 221-223°C. ^{1}H-NMR (500 MHz, DMSO-d6): 9.05(1H,br s), 8.90(1H,br s), 8.32 (1H,s), 6.24 (1H, s), 5.67 (1H,m), 3.48 (1H, m), 3.41 (1H,m), 3.33(2H, m), 2.58(3H,s), 2.26 (1H,m), 2.17 (1H,m). M+1= 304.2

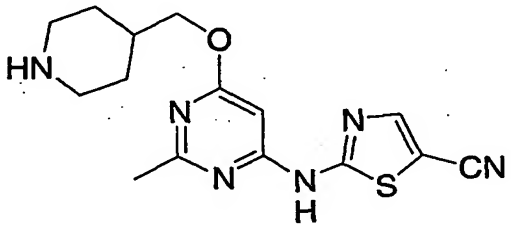
Synthesis of 2-({2-methyl-6-[(3S)-pyrrolidin-3-yloxy]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile (2-6)



2-6

The title compound was prepared according to the procedure described in Scheme 2 except tert-butyl-(3S)-3-hydroxypyrrolidine-1-carboxylate was substituted for tert-butyl-4-hydroxy-piperidine-1-carboxylate. This product was obtained as the TFA salt, mp: 222-224°C. ^{1}H-NMR (500 MHz, DMSO-d6): 9.06 (1H,br s), 8.94(1H,br s), 8.32 (1H,s), 6.24 (1H, s), 5.67 (1H,m), 3.48 (1H, m), 3.41 (1H,m), 3.33(2H, m), 2.58(3H,s), 2.26 (1H,m), 2.17 (1H,m). M+1= 304.2

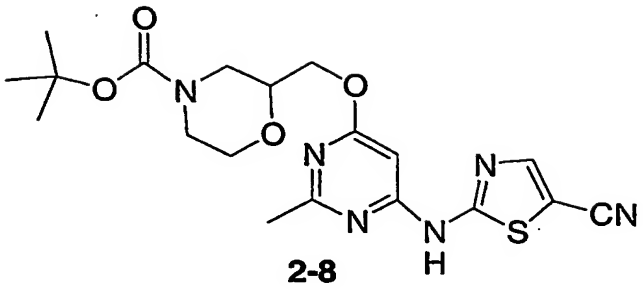
Synthesis of 2-{[2-methyl-6-(piperidin-4-ylmethoxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile (2-7)



2-7

The title compound was prepared according to the procedure described Scheme 2 except tert-butyl-4-hydroxymethyl-piperidine-1-carboxylate was substituted for tert-butyl-4-hydroxy-piperidine-1-carboxylate. This product was obtained as the TFA salt. ^{1}H-NMR (500 MHz, DMSO-d6): 8.57(1H,br s), 8.32 (1H, s), 8.22(1H, br s), 6.22 (1H,s), 4.22 (2H, d, J=6.3Hz), 3.30 (2H, m), 2.91 (2H, m), 2.56 (3H, s), 2.06 (1H, m), 1.91 (2H, d, J=13.9 Hz), 1.45 (2H, q, J=12.5 Hz). M+1 = 331.3

Synthesis of tert-Butyl 2-[({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}oxy)methyl]-morpholine-4-carboxylate (2-8)

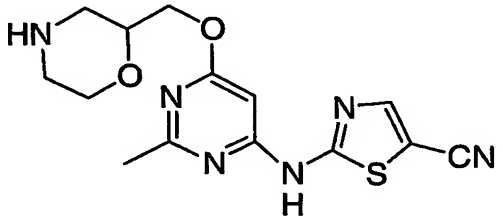


2-8

A solution of 1 M borane/THF (6 mL, 6 mmol) was added dropwise to a solution of racemic 4-(tert-butoxycarbonyl)morpholine-2-carboxylic acid (693 mg, 3 mmol) in THF (6 mL) which was cooled in a ice bath. Let stir at ambient temperature over night and then quenched reaction by careful addition of methanol (3 mL). Saturated aqueous sodium sulfate (~1 mL) was added to this reaction, followed by solid sodium sulfate. The precipitate was removed by filtration and the organic solution was evaporated under reduced pressure. The residue was diluted with methanol and the solvent evaporated (2X). To remove traces of water, the residue was dissolved in toluene and the solvent removed to give racemic tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate as a viscous oil which was used as is.

The title compound was prepared according to the procedure described in Scheme 2 except racemic tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate was substituted for tert - butyl 4-hydroxy-piperidine-1-carboxylate. The racemic product was obtained as a white crystalline solid, mp: 233-235 C. ^{1}H-NMR (500 MHz, $CDCl_3$): 9.55 (1H, br s), 7.96 (1H,s), 7.26 (1H,s), 4.44 (2H,d, J=4.6 Hz), 4.06 (1H, br s), 3.95 (2H, d, J=10.2 Hz), 3.88 (1H, br s), 3.79 (1H, br s), 3.59 (1H, t, J=11Hz), 3.01 (1H, br s), 2.82 (1H, br s), 2.63 (3H, s), 1.48 (9H,s). M+1 = 433.4

Synthesis of 2-{[2-Methyl-6-(morpholin-2-ylmethoxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile (**2-9**)

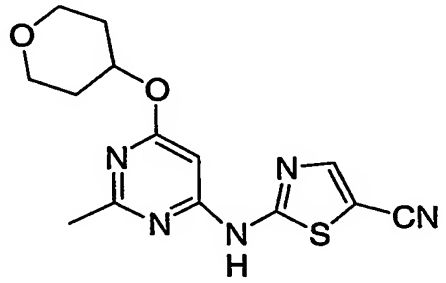


2-9

The title compound was prepared according to the procedure described in Scheme 2 using compound **2-8** above. This racemic product was obtained as the TFA salt, mp: 241-

242°C. ^{1}H-NMR (500 MHz, DMSO-d6): 12.3(1H, br s), 8.93(1H,br s), 8.32(1H, s), 6.24 (1H,s), 4.39 (2H, m), 4.01(2H, dd, J=3 Hz, J=12 Hz), 3.72 (1H, t, J=11 Hz), 3.33 (1H, d, J=3 Hz), 3.21 1H, d, J=3 Hz), 2.94-3.06 (2H, m), 2.56 (3H,s). M+1 = 333.4

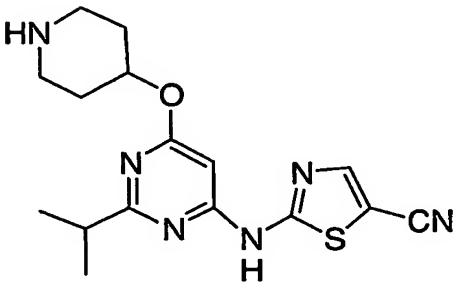
Synthesis of 2-{[2-Methyl-6-(tetrahydro-2-pyran-4-yloxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile (**2-10**)



2-10

The title compound was prepared according to the procedure described in Scheme 2 except tetra-hydro-2H-pyran-4-ol was substituted for tert -butyl 4-hydroxy-piperidine-1-carboxylate. This product was obtained as the TFA salt, mp: >260 C. ^{1}H-NMR (500 MHz, DMSO-d6): 12.16(1H,br s), 8.30 (1H,s), 6.19 (1H, s), 5.25 (1H,m), 3.84 (2H, m), 3.51 (2H,t, J=11.7 Hz), 2.54 (3H, s), 1.98 (2H,m), 1.64 (2H,m). M+1= 318.3

Synthesis of 2-{[2-Isopropyl-6-(piperidin-4-yloxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile (**2-11**)



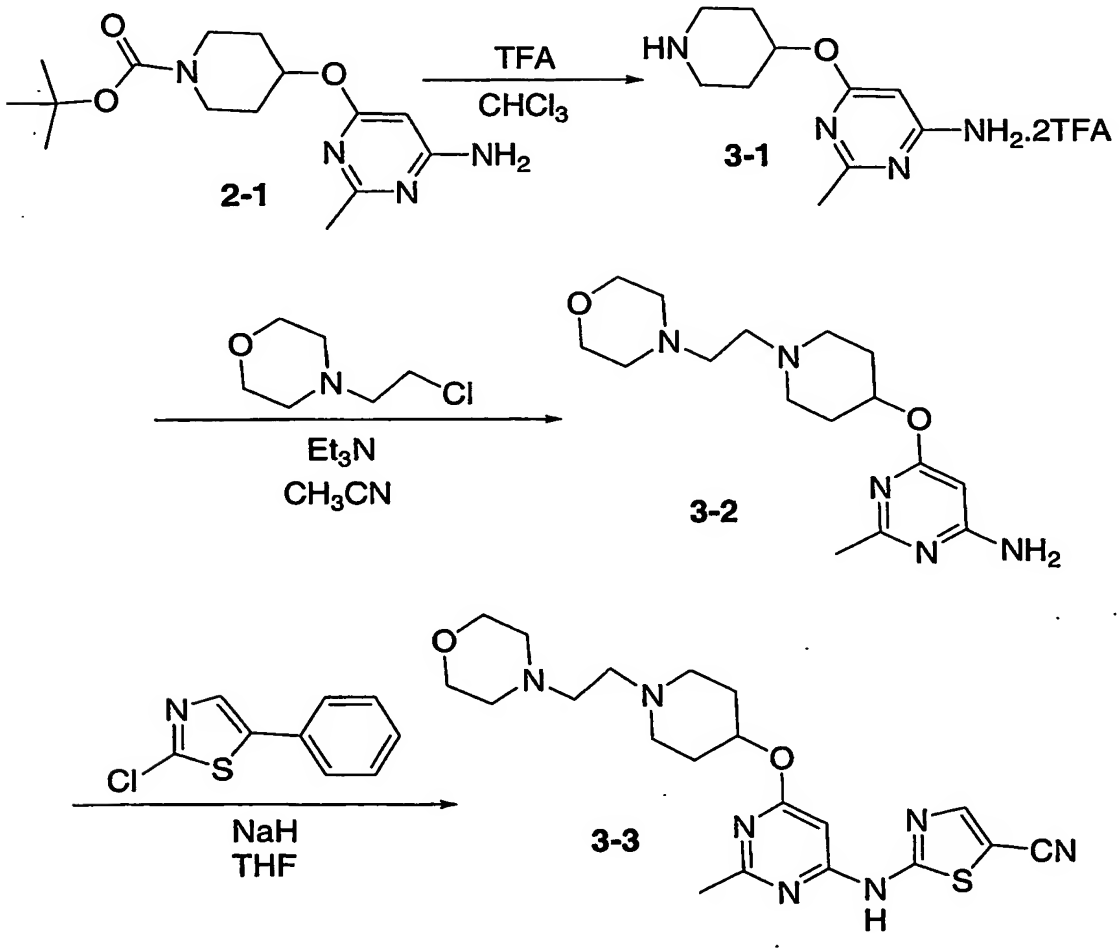
2-11

A mixture of 2-isopropyl-4,6-dichloropyrimidine (1.3 gm, 6.8 mmol), which is obtained according to the procedures described in Aust. J. Chem., 30, 1785-91(1977), in conc. aq. ammonium hydroxide (10 mL) and n-butanol (10 mL) was sealed in a screw-top vessel and

heated at 90°C for four hours. The cooled mixture was extracted into ethyl acetate, washed with water and the organic layer dried over anhydrous sodium sulfate. The filtered solution was evaporated to a small volume and diluted with diethyl ether as the product, 6-chloro-2-isopropylpyrimidin-4-amine, crystallized out, mp: 194-196°C. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.28 (1H, s), 4.90 (2H, br s), 3.96 (1H,m), 1.27 (6H, d, J=6.8 Hz).

The title compound was prepared according to the procedure described in Scheme 2 except 6-chloro-2-isopropylpyrimidin-4-amine was substituted for 6-chloro-2-methylpyrimidin-4-amine. This product was obtained as the TFA salt, mp: 234-235°C. ^{1}H-NMR (500 MHz, DMSO-d6): 12.21 (1H, s), 8.54 (1H, br s), 8.48(1H, br s), 8.32(1H,s), 6.23 (1H,s), 5.32(1H,m), 3.46(2H,m), 3.15 (2H,m), 3.05 (1H, m), 2.13(2H,m), 1.89 (2H,m), 1.34 (6H, d, J=6.8 Hz). M+1= 345.4

SCHEME 3



Synthesis of 2-methyl-6-(piperidin-4-yloxy)pyrimidin-4-amine (3-1)

A solution of tert-butyl-4-[(6-amino-2-methylpyrimidin-4-yl)oxy] piperidine-1-carboxylate (2-1) (200 mg, 0.65 mmol) in chloroform (5 mL) containing TFA (0.25 mL) was stirred at room temperature for three hours. The solvents were evaporated and the residue was chased with chloroform (2X). The residue was triturated with diethyl ether and allowed to stir over night. The title compound was collected and determined to be the bis-TFA salt. This material was used as is. ^{1}H-NMR (500 MHz, DMSO-d_6): 8.55 (1H, br s), 8.50 (1H, br s), 7.34 (1H, br s), 5.73 (1H, s), 5.18 (1H, m), 3.22 (2H, m), 3.12 (2H, m), 2.34 (3H,s), 2.08 (2H,m), 1.83 (2H, m).

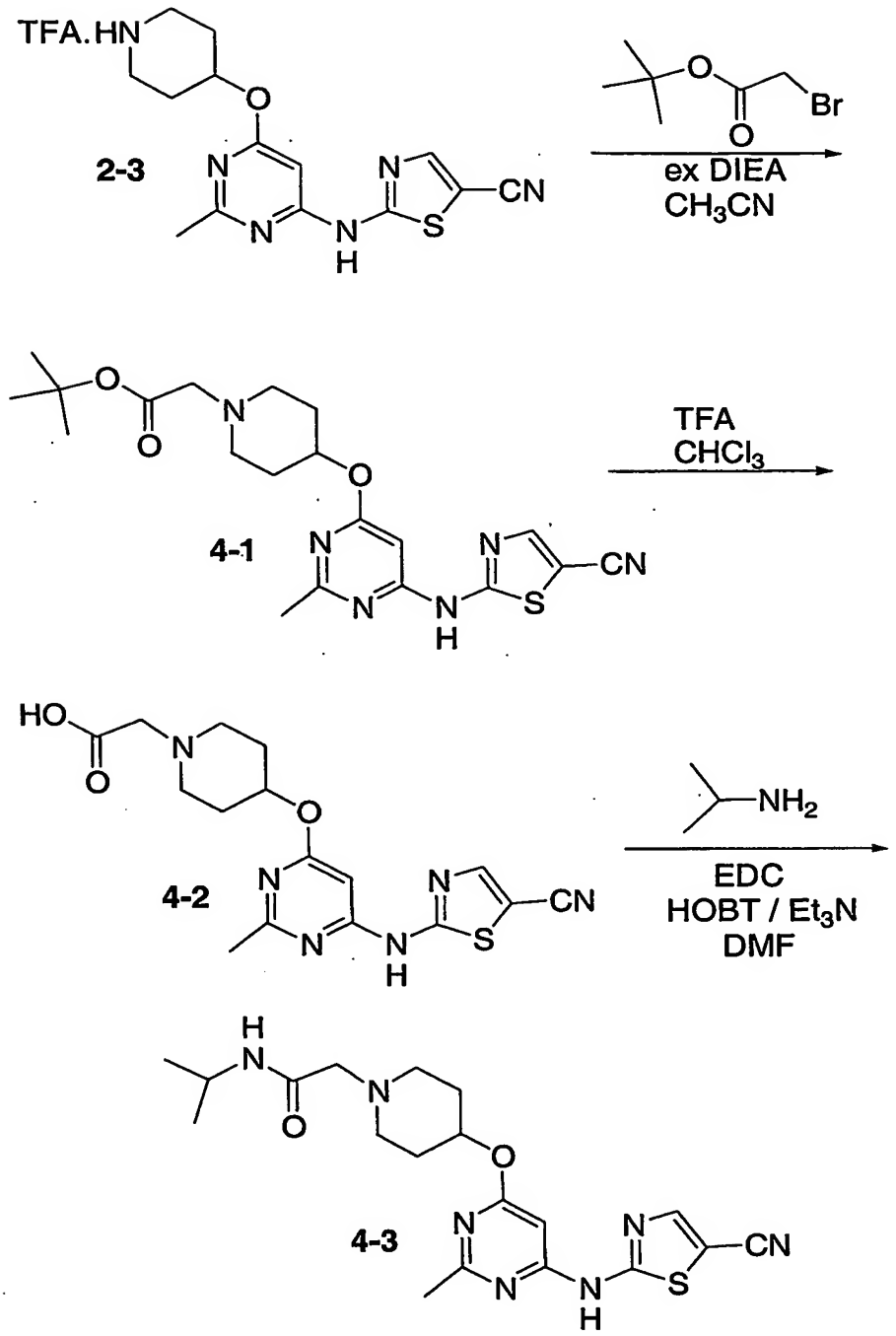
Synthesis of 2-methyl-6-{[1-(2-morpholin-4-ylethyl)piperidin-4-yl]oxy}pyrimidin-4-amine (3-2)

A clear solution was obtained when triethylamine (0.45 mL, 3.2 mmol) was added to a suspension of 2-methyl-6-(piperidin-4-yloxy)pyrimidin-4-amine bis-TFA salt (264 mg, 0.60 mmol) in acetonitrile (5 mL). Then 4-(2-chloroethyl) morpholine hydrochloride (122 mg, 0.65 mmol) was added to the reaction and this solution was heated at 80°C over night. The cooled mixture was evaporated to remove the solvent and the residue was purified by chromatography on silica gel eluting with a 1-8% methanol/ethyl acetate gradient. The appropriate fractions were combined and the solvent removed under vacuum. This residue was triturated with diethyl ether to give solid product. This material was used as is. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.58 (1H, s), 5.03 (1H, m), 4.06 (2H, br s), 3.72 (4H, m), 2.77(2H, m), 2.54 (4H, br s), 2.50 (4H,br s), 2.41 (3H,s), 2.35 (2H, br t, J=8.6Hz), 2.01 (2H,m), 1.79 (2H, m). M+1 = 322.3

Synthesis of 2-[(2-methyl-6-{[1-(2-morpholin-4-ylethyl)piperidin-4-yl]oxy} pyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile (3-3)

The title compound was prepared according to the procedure described in Scheme 2 for compound 2-2, except 2-methyl-6-{[1-(2-morpholin-4-ylethyl) piperidin-4-yl]oxy}pyrimidin-4-amine was substituted for tert-butyl-4-[(6-amino-2-methylpyrimidin-4-yl)oxy]piperidine-1-carboxylate. The pure product was obtained after chromatography on silica gel (eluting with a 1-10% methanol/ chloroform saturated with ammonium hydroxide) and crystallization from methanol, mp: 238-240°C. ^{1}H-NMR (500 MHz, DMSO-d_6): 8.80(1H,br s), 7.93 (1H,s), 5.94 (1H, s), 5.17 (1H, m), 3.72 (4H,m), 2.79 (2H, m), 2.61 (3H, s), 2.55 (4H, br s) 2.50 (4H,br s), 2.37 (2H, br t, J=8.6Hz), 2.02 (2H,m), 1.82 (2H, m). M+1= 430.2

SCHEME 4



Synthesis of tert-butyl-[4-({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}oxy)piperidin-1-yl]acetate (4-1)

Diisopropylethylamine (0.21 mL, 1.2 mmol) was added to a suspension of 2-{[2-methyl-6-(piperidin-4-yloxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile TFA salt (**2-3**) (165 mg, 0.38 mmol) in dry acetonitrile(4 mL) to give a clear solution. Tert-butyl bromoacetate (0.07 mL, 0.45 mmol) was then added and the solution was heated to 80°C for 1.25 hours. Upon cooling to room temperature the product began to crystallize out. Most of the title compound was obtained by filtration from the reaction mixture. Additional material was recovered from the mother liquors by chromatography on silica gel and elution with a 40-60% ethyl acetate/hexane gradient. This material was used as is. ^{1}H-NMR (500 MHz, $CDCl_3$): 9.50 (1H, br s), 7.95(1H, s), 5.96 (1H, s), 5.20 (1H, m), 3.17 (2H, s), 2.85 (2H, m), 2.61 (3H, s), 2.52 (2H, br t, J=10Hz), 2.05 (2H, m), 1.88 (2H, m), 1.48 (9H, s). M+1 = 431.3

Synthesis of [4-({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}oxy) piperidin-1-yl]acetic acid (**4-2**)

A solution of tert-butyl-[4-({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}oxy)piperidin-1-yl]acetate (107 mg, 0.25 mmol) in chloroform (5 mL) containing TFA (1 mL) was stirred at room temperature over night. The solvent was evaporated and the residue chased with chloroform (2X). Then upon trituration with diethyl ether the title compound was obtained as a solid TFA salt. This material was used as is. ^{1}H-NMR (500 MHz, DMSO-d_6): 8.31 (1H, s), 6.21 (1H, s), 5.25 (1H, m), 3.76 (2H, br s), 3.20 (2H, br s), 3.07 (2H, br s), 2.55 (3H, s), 2.12 (2H, br s), 1.93 (2H, br s). M+1 = 375.1

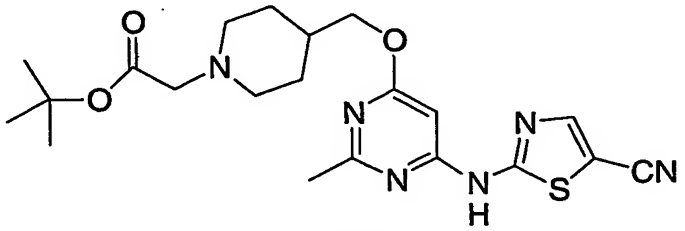
Synthesis of 2-[4-({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl} oxy)piperidin-1-yl]-N-isopropylacetamide (**4-3**)

To a suspension of [4-({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}oxy)- piperidin-1-yl]acetic acid TFA salt (107 mg, 0.21 mmol) in dry DMF (2 mL) was added triethylamine (0.085 mL, 0.60 mmol), isopropyl amine (0.21 mL, 0.23 mmol), 1-hydoxybenzotriazole hydrate (31 mg, 0.3 mmol) and finally 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC)(51 mg, 0.26 mmol). This reaction mixture was stirred at room temperature over night. The reaction was diluted with ethyl acetate, washed with water, and the organic layer dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. The residue was triturated with diethyl ether and the title compound slowly crystallized out of solution. This semi-pure material was dissolved in chloroform and some TFA was added to form the TFA salt. Upon evaporation of the solvent and trituration of the residue with diethyl ether the TFA salt was obtained as a white solid, mp: 226-228°C.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.97(1H, s), 7.01(1H, d, J= 8 Hz), 6.00(1H, s), 5.22(1H, m), 4.12(1H, m), 3.02(2H, s), 2.77(2H, m), 2.62(3H, s), 2.46(2H, m), 2.04(2H, br s), 1.84(2H, br s), 1.18(2H, d, J=6.4Hz). M+1 = 416.2

Compounds **4-4** through **4-6** below were synthesized via the same protocol shown in Scheme 4 by using the appropriately substituted piperidine and an amine.

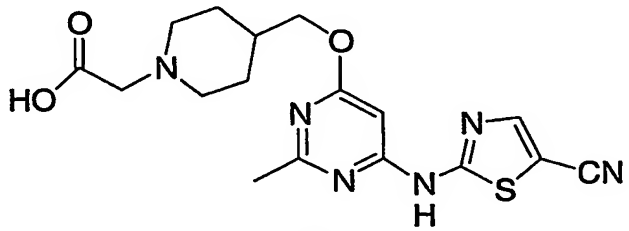
Synthesis of Tert-Butyl{4-[({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}oxy)methyl]piperidin-1-yl}acetate (**4-4**)



4-4

The title compound was prepared according to the procedure described in Scheme 4 except 2-{[2-methyl-6-(piperidin-4-ylmethoxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile TFA salt (**2-7**) was substituted for 2-{[2-methyl-6-(piperidin-4-yloxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile TFA salt (**2-3**). This product was obtained as the freebase, mp: 210-212°C. ^{1}H-NMR (500 MHz, $CDCl_3$): 9.45(1H,br s), 7.95(1H, s), 5.95 (1H,s), 4.21 (2H, d, J=5.9Hz), 3.31 (2H, s), 3.00 (2H, d, J=11.2 Hz),2.62 (3H, s), 2.20 (2H, t, J=11.2 Hz), 1.79 (3H, d, J=11.2 Hz), 1.50 (2H,m),1.47 (9H, s). M+1 = 445.4

Synthesis of {4-[({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}oxy) methyl]piperidin-1-yl}acetic acid (**4-5**)

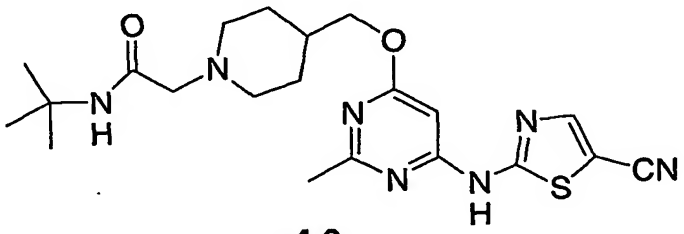


4-5

The title compound was prepared according to the procedure described in Scheme 4 from tert-butyl {4-[({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}oxy)methyl]piperidin-1-yl} acetate (**4-4**) above. This product was obtained as the zwitterionic

freebase, mp: >250°C. ^{1}H-NMR (500 MHz, DMSO-d_6): 12.19(1H,br s), 8.31(1H, s), 6.21 (1H,s), 4.18 (2H, d, J=6.3Hz), 3.21 (4H, m), 2.58 (2H, m), 2.56 (3H, s), 1.86 (1H, m), 1.78 (2H, d, J=13.2 Hz), 1.47 (2H, m). M+1 = 388.3 (very weak), 156.2 (M – 233)

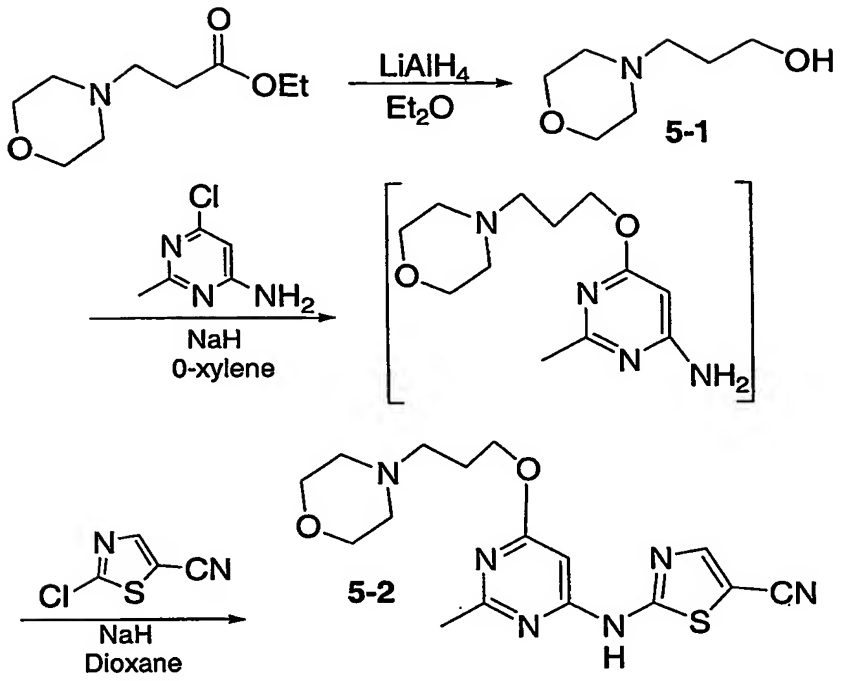
Synthesis of N-(tert-Butyl)-2-{4-[({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}oxy)methyl]piperidin-1-yl}acetamide (**4-6**)



4-6

The title compound was prepared according to the procedure described in Scheme 4 except {4-[({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}oxy)methyl]piperidin-1-yl}acetic acid (**4-5**) above was substituted for [4-({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}oxy)- piperidin-1-yl]acetic acid TFA salt (**4-2**) and tert-butyl amine was substituted for isopropyl amine. This product was obtained as the freebase, mp: 248-249°C. ^{1}H-NMR (500 MHz, $CDCl_3$): 12.16(1H,br s), 8.29(1H, s), 7.14 (1H, br s), 6.19 (1H,s), 4.15 (2H, d, J=6.1Hz), 3.32 (4H, s), 2.54 (3H, s), 2.07 (2H, t, J=10.5 Hz), 1.71 (2H, d, J=11.5 Hz), 1.29 (2H, m),1.27 (9H, s). M+1 = 444.4

SCHEME 5



Synthesis of 3-morpholin-4-ylpropan-1-ol (**5-1**)

Ethyl 3-morpholin-4-ylpropanoate (2.0 gm, 10.68 mmol) was dissolved in ether (200 mL). A 1 M solution of lithium alumumhydride in ether (11.0 mL, 11.0 mmol) was added dropwise and the reaction allowed to stir for 2.5 hours. Saturated sodium sulfate was added and the reaction allowed to stir over night. Solid sodium sulfate was then added and the reaction filtered. Solvent removal yielded 3-morpholin-4-ylpropan-1-ol. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.00(1H,br s), 3.82(2H, t, J=5.37hz), 3.71(4H, t, J=4.39), 2.62(4H, t, J=5.86hz), 2.53(4H, br s), 1.74(2H, m). M+1=146

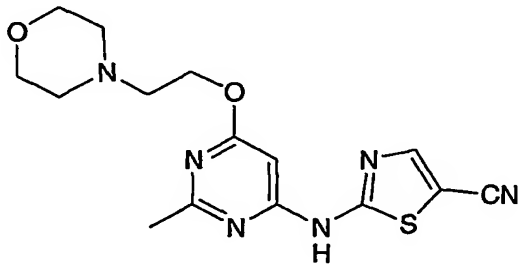
Synthesis of 2-{[2-methyl-6-(3-morpholin-4-ylpropoxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile (**5-2**)

Sodium hydride (60% in mineral oil, 34.5 mg, 0.86 mmol) was added to a mixture of o-xylene (3.0 mL) and 3-morpholin-4-ylpropan-1-ol (100 mg, 0.69 mmol). After the effervescence had stopped the 6-chloro-2-methylpyrimidin-4-amine (98.9 mg, 0.69 mmol) was added and the reaction heated at 130°C over night. The excess o-xylene was removed under vacuum and the residue dissolved into dry dioxane and sodium hydride (60% in mineral oil, 34.5 mg, 0.86 mmol) was then added. After the effervescence had stopped 2-chloro-1,3-thiazole-5-carbonitrile (99.6 mg, 0.69 mmol) was added and the reaction heated at 100°C over night. The

dioxane was removed and the residue treated with trifluoroacetic acid (2 drops) and methanol (4.0 mL). This was then purified using preparative HPLC to give 2-{[2-methyl-6-(3-morpholin-4-ylpropoxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile as the trifluoroacetic acid salt. ^{1}H-NMR (500 MHz, DMSO-d6): 12.40 (1H, br s), 9.83 (1H, s), 8.31 (1H, s) 6.23 (1H, s), 4.39 (2H, t, J=5.86hz), 4.00 (2H, d, J=12.45Hz), 3.65 (2H, t, J=11.96Hz), 3.48 (2H, d, J=12.70Hz), 3.27 (2H, br s), 3.09 (2H, br s), 2.56 (3H, s), 2.13 (2H, m). High res. ES MS: Theoretical Mass 361.1441, Measured Mass 61.1446 ($C_{16}H_{20}N_6O_2S+H^+$)

Compounds **5-3** through **5-4** were synthesized via the same protocol shown in Scheme 5 by using an appropriate alcohol.

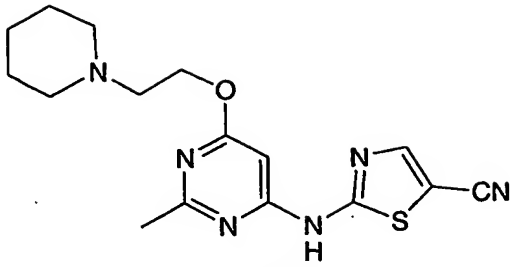
Synthesis of 2-{[2-methyl-6-(2-morpholin-4-ylethoxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile (5-3)



5-3

The title compound was prepared according to scheme 5, except 2-morpholin-4-ylethanol was substituted for 3-morpholin-4-yl propan-1-ol to obtain 2-{[2-methyl-6-(2-morpholin-4-ylethoxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile as the trifluoroacetic acid salt. ^{1}H-NMR (500 MHz, CD_3OD): 8.04 (1H, s) 6.26 (1H, s), 4.78 (2H, t, J=5.13hz), 4.07 (2H, br s), 3.56 (2H, br s), 3.66 (2H, t, J=6.84Hz), 3.62 (2H, br s), 3.30 (2H, br s), 3.17 (3H, s). High res. ES MS: Theoretical Mass 347.1285, Measured Mass 347.1243 ($C_{15}H_{18}N_6O_2S+H^+$)

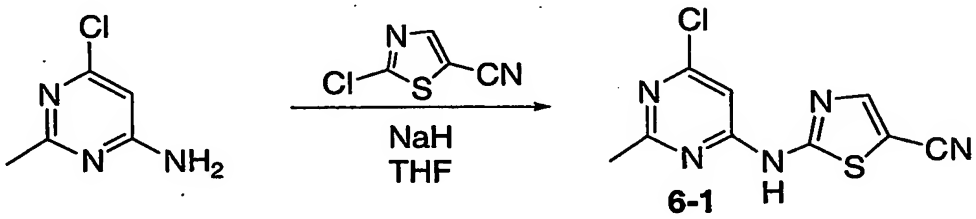
Synthesis of 2-{[2-methyl-6-(2-piperidin-1-ylethoxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile (5-4)



5-4

The title compound was prepared according to Scheme 5, except 2-piperidin-1-ol was substituted for 3-morpholin-4-yl propan-1-ol to obtain 2-{[2-methyl-6-(2-piperidin-1-ylethoxy)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile as the trifluoroacetic acid salt ^{1}H-NMR (500 MHz, CD_3OD): 8.04 (1H, s) 6.25 (1H, s), 4.75 (2H, t, J=5.13hz), 3.66 (2H, d J=12.21Hz), 3.57 (2H, t, J=5.12Hz), 3.05 (2H, t, J=12.69Hz), 1.97 (2H, d, J=15.14Hz), 1.82 (3H, m), 1.54 (1H, m). M+1 = 345.0

SCHEME 6

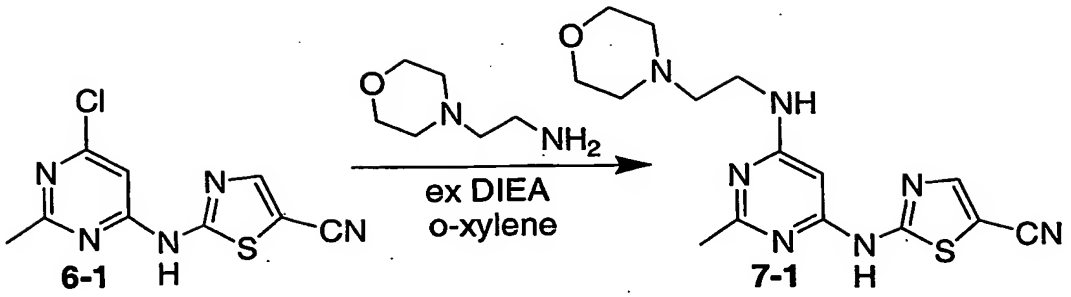


6-1

Synthesis of 2-[(6-chloro-2-methylpyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile (**6-1**)

6-Chloro-2-methylpyrimidin-4-amine (144.0 mg, 1.0 mmol), which is prepared from 6-amino-2-methylpyrimidin-4-ol as described in *Chem. Ber.*, 75, 755(1942), was added to the reaction flask along with dioxane (3.0 mL), and sodium hydride (60% in mineral oil, 120 mg, 3.0 mmol). After the effervescence had subsided 2-chloro-1,3-thiazole-5-carbonitrile (145.0 mg, 1.0 mmol) was added. After 2.0 hours the heat was removed and the reaction allowed to stir over night. The reaction was diluted with water then, acidified with concentrated HCl. The pH was adjusted to 8 with sodium bicarbonate and the aqueous layer extracted with ethyl acetate (3x100mL). The combined extracts were washed with brine (1x25mL) and dried ($MgSO_4$). Solvent removal yielded the desired 2-[(6-chloro-2-methyl-pyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile. ^{1}H-NMR (500 MHz, DMSO-d_6): 12.74 (1H,s), 8.38 (1H,s), 6.95 (1H, s), 2.62 (3H, s). M + 1=252

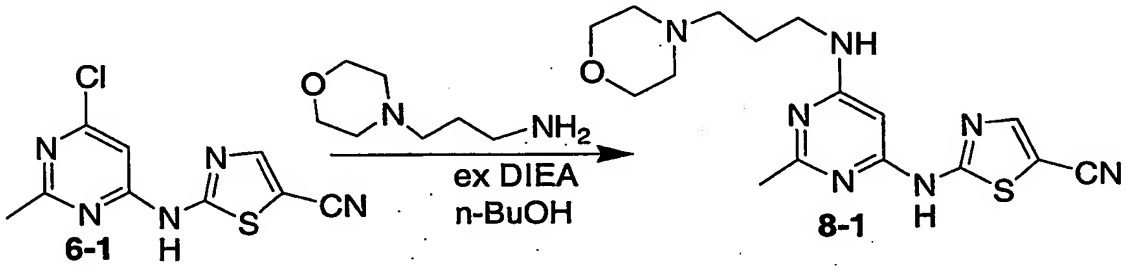
SCHEME 7



Synthesis of 2-({2-methyl-6-[(2-morpholin-4-ylethyl)amino]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile (7-1)

2-[(6-Chloro-2-methylpyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile (**6-1**)(75.0 mg, 0.30 mmol) was added to a reaction flask along with o-xylene (3.0 mL), diisopropylethyl amine (154.1 mg, 1.19 mmol) and 4-(2-aminoethyl)morpholine (77.6 mg, 0.60 mmol). The reaction was heated over night at 120°C. The o-xylene was removed under high vacuum and the residue dissolved into methanol (4.0 mL) and purified by preparative HPLC. This gave 2-({2-methyl-6-[(2-morpholin-4-ylethyl)amino]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile as the trifluoroacetic acid salt. ^{1}H-NMR (500 MHz, CD_3OD): 8.01 (1H, s) 6.01 (1H, s), 3.94 (4H, br s), 3.81(2H, t, J=5.86Hz), 3.46(4H, br s), 3.41(2H, t, J=5.61Hz), 2.56 (3H, s). M+1 = 346.0

SCHEME 8



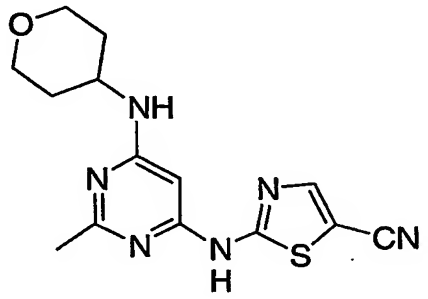
Synthesis of 2-({6-[(3-morpholin-4-ylpropyl)amino]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile (8-1)

2-[(6-Chloro-2-methylpyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile (**6-1**) (75.0 mg, 0.298 mmol) was added to a reaction flask along with 3-morpholin-4-ylpropan-1-amine (171.9 mg, 1.19 mmol), N,N-diisopropylethylamine (231 mg, 1.79 mmol), and N-butanol (3.0 mL). The reagents were heated over night at 120°C. The reaction was cooled and excess

solvents removed. The residue was then purified on a preparative HPLC. This gave the desired 2-({6-[(3-morpholin-4-ylpropyl)amino]-pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile as the trifluoroacetic acid salt. ^{1}H-NMR (500 MHz, DMSO-d6): 12.00 (1H, br s), 8.24 (1H, s), 7.50 (1H,br s) 5.90 (1H, br s), 3.98 (2H, br s), 3.66 (2H, br s), 3.43 (2H, br s), 3.34 (2H, br s), 3.16 (2H, br s), 3.07 (2H, br s), 2.41 (3H, s), 1.90 (2H, br s). M+1 = 346.0

Compounds **8-2** through **8-6** were synthesized via the same protocol shown in Scheme 5 by using an appropriate amine.

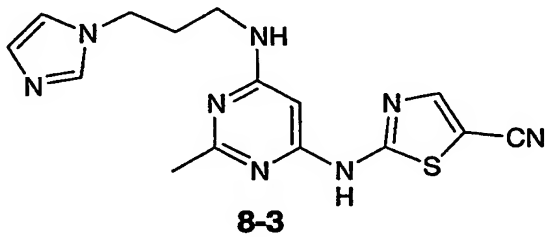
Synthesis of 2-{[2-methyl-6-(tetrahydro-2*H*-pyran-4-ylamino)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile (**8-2**)



8-2

The title compound was prepared according to the protocol described in Scheme 8, except tetrahydro-2*H*-pyran-4-amine was substituted for 3-morpholin-4-ylpropan-1-amine. 2-{[2-Methyl-6-(tetrahydro-2*H*-pyran-4-ylamino)pyrimidin-4-yl] amino}-1,3-thiazole-5-carbonitrile was obtained as the freebase, mp; >250°C. ^{1}H-NMR (500 MHz, DMSO-d6): 11.50 (1H, s), 8.22 (1H, s), 7.33 (1H, d, J=7.8 Hz), 5.89 (1H, s), 3.85 (1H, d, J=8.3Hz), 3.39 (2H, t, J=11.3 Hz), 2.39(3H, s), 1.82 (2H, d, J=12.5 Hz), 1.42 (2H, br q). M+1 = 317.3

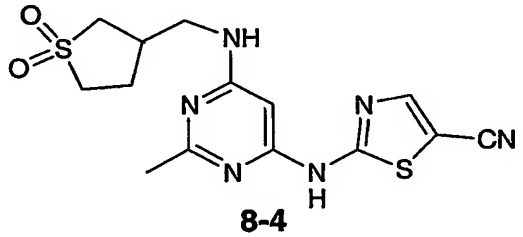
Synthesis of 2-[(6-{[3-(^{1}H-imidazol-1-yl)propyl]amino}-2-methylpyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile (**8-3**)



8-3

3-(1H-imidazol-1-yl)propan-1-amine (49.7 mg, 0.40 mmol) was treated with excess N,N-diisopropyl-ethylamine (308 mg, 2.38 mmol) along with 2-[(6-chloro-2-methylpyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile (**6-1**) (100 mg, 0.40 mmol) and n-butanol (2.0 mL). The reaction was heated for 18 hours at 100°C. The reaction was cooled and filtered. The solid was then washed with water, additional butanol, and ether. This gave 2-[(6-{[3-(1H-imidazol-1-yl)propyl]amino}-2-methylpyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile as a tan solid freebase. ^{1}H-NMR (500 MHz, DMSO-d6): 11.09 (1H, br s), 8.22 (1H, s), 7.64 (1H, s), 7.40 (1H, t J=5.62Hz), 7.20 (1H, t J=1.22Hz), 6.89 (1H, s), 5.86 (1H, br s), 4.02 (2H, t J=6.84Hz), 3.17 (2H, br s), 2.39 (3H, s), 1.95 (2H, m J=6.83Hz). M+1 = 341

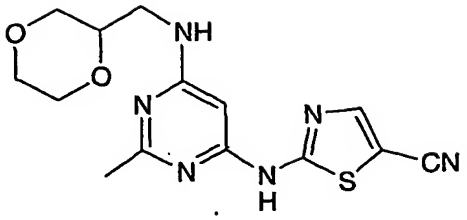
Synthesis of 2-[(6-{[(1,1-dioxidotetrahydrothien-3-yl)methyl]amino}-2-methylpyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile (**8-4**)



8-4

Racemic 1-(1,1-dioxidotetrahydrothien-3-yl)methanamine (60 mg, 0.40 mmol) was added to a flask along with excess N,N-diisopropylethylamine (308 mg, 2.38 mmol), 2-[(6-chloro-2-methylpyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile (**6-1**) (100 mg, 0.40 mmol), and n-butanol (2.0 mL). The reaction was heated for 18 hours at 100°C. Additional amine and DIEA were added (1eq/3eq) and the reaction was allowed to continue to heat for an additional 18 hours. The solvents were removed and the residue purified on a prep HPLC. This gave 2-[(6-{[(1,1-dioxidotetrahydrothien-3-yl)methyl]amino}-2-methylpyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile as the trifluoroacetic acid salt. ^{1}H-NMR (500 MHz, DMSO-d6): 11.98 (1H, br s), 8.23 (1H, s), 7.55 (1H, br s), 5.92 (1H, br s), 3.41 (2H, br s), 3.21 (2H, m), 3.21 (2H, m), 3.06 (1H, m), 2.85 (1H, m), 2.64 (1H, m), 2.41 (3H, s), 2.23 (1H, br s), 1.83 (1H, m). M+1 = 365

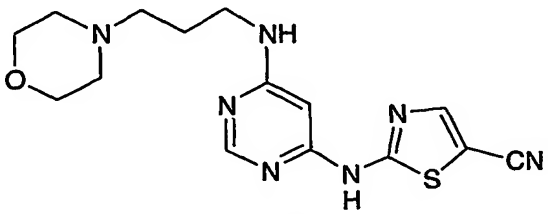
Synthesis of 2-({6-[(1,4-dioxan-ylmethyl)amino]-2-methylpyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile (**8-5**)



8-5

Racemic 1,4-dioxan-2-ylmethylamine (46 mg, 0.40 mmol) was added to a flask along with excess N,N-diisopropylethylamine (308 mg, 2.38 mmol), n-butanol (2.0 mL) and 2-[(6-chloro-2-methylpyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile (**6-1**) (100 mg, 0.40 mmol). The reaction heated for 18 hours at 100°C. The solvents were removed and the residue purified on the prep HPLC. This yielded 2-({6-[(1,4-dioxan-2-ylmethyl)amino]-2-methylpyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile as the trifluoroacetic acid salt. ^{1}H-NMR (500 MHz, DMSO-d6): 12.01 (1H, br s), 8.23 (1H, s), 7.53 (1H, br s), 5.98 (1H, br s), 3.74 (2H, d J=11.72 Hz), 3.64 (2H, d J=11.23Hz), 3.57 (1H, t J=11.23), 3.46 (1H, t J=11.23Hz), 3.32 (2H, br s), 3.25 (1H, t J=11.48Hz), 2.42 (3H, s). M+1 = 333

Synthesis of 2-({6-[(3-morpholin-4-ylpropyl)amino]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile (**8-6**)

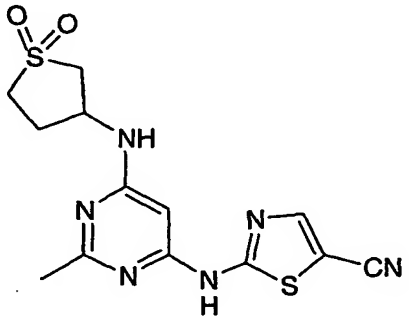


8-6

3-Morpholin-4-ylpropan-1-amine (182 mg, 1.26 mmol) was added to a flask with excess N,N-diisopropylethylamine (327 mg, 2.53 mmol) along with 2-[(6-chloropyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile (100 mg, 0.421 mmol), and n-butanol (2.0 mL). The reaction heated for 18 hours at 100°C. The reaction was cooled and diluted with ethyl acetate (50 mL). The ethyl acetate layer was washed with brine/water (50/10 mL). The organic layer was dried with $MgSO_4$ and the solvent removed to yield a gum. The gum was placed on the prep HPLC and purified in the usual way. This gave 2-({6-[(3-morpholin-4-ylpropyl)amino]pyrimidin-4-yl} amino)-1,3-thiazole-5-carbonitrile as the trifluoroacetic salt. ^{1}H-NMR (500 MHz, DMSO-d6): 12.05 (1H, br s), 9.78 (1H, br s), 8.25 (1H, s), 7.61 (1H, br s),

6.08 (1H, br s), 3.97 (2H, br s), 3.64 (2H, br s), 3.42 (2H, br s), 3.38 (2H, br s), 3.15 (2H, br s), 3.07 (2H, br s), 1.90 (2H, br s). M+1 = 346

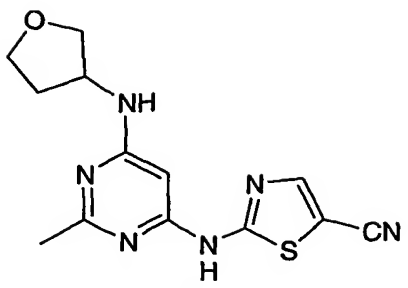
Synthesis of 2-({6-[(1,1-Dioxidotetrahydrothien-3-yl)amino]-2-methylpyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile (8-7)



8-7

2-[(6-Methoxy-2-methylpyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile (100.0 mg, 0.397 mmol) was added to a reaction flask along with 1,1-dioxidotetrahydrothien-3-ylamine (107.3 mg, 0.79 mmol), N-ethyl-N,N-diisopropylamine (410 µL, 2.38 mmol) and n-butanol (3.0 mL). The reaction was heated at reflux for one week. The reaction was cooled and the n-butanol was removed. The residue was treated with trifluoroacetic acid (0.5 mL) and diluted with methanol (3.0 mL). The mixture was then purified on a preparative high pressure chromatograph. This yielded 2-({6-[(1,1-dioxidotetrahydro-thien-3-yl)amino]-2-methylpyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile as the trifluoroacetic acid salt. ^{1}H-NMR (500 MHz, DMSO-d_6): 12.03 (1H, br s), 8.24 (1H, br s) 7.79 (1H, br s), 5.97 (1H, br s), 4.62 (1H, br s), 3.53 (1H, br s), 3.34 (1H, br s), 3.21 (1H, br s), 2.19 (1H, br s), 2.51 (1H, br s), 2.43 (3H, s), 2.12 (1H, br s). M+1 = 351

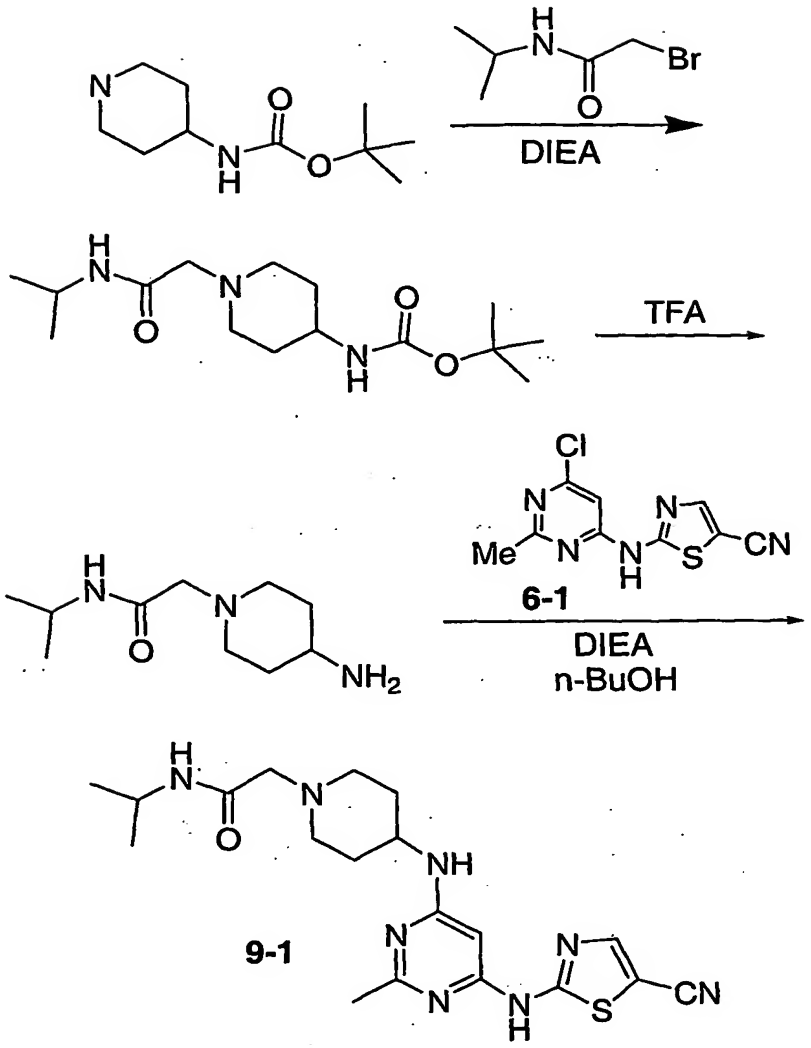
2-{[2-Methyl-6-(tetrahydrofuran-3-ylamino)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile (8-8)



8-8

2-[(6-Methoxy-2-methylpyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile (100.0 mg, 0.397 mmol) was added to a reaction flask along with tetrahydrofuran-3-amine hydrochloride salt (136.3 mg, 0.79 mmol), N-ethyl-N,N-diisopropylamine (410 μL, 2.38 mmol) and n-butanol (3.0 mL). The reaction was heated at reflux for one week. The reaction was cooled and the n-butanol was removed. The residue was treated with trifluoroacetic acid (0.5 mL) and diluted with methanol (3.0 mL). The mixture was then purified on a preparative high pressure chromatograph. This yielded 2-{[2-methyl-6-(tetrahydro-furan-3-ylamino)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile as the trifluoroacetic acid salt. ^{1}H-NMR (500 MHz, DMSO-d$_6$): 11.99 (1H, br s), 8.23 (1H, s) 7.65 (1H, br s), 5.93 (1H, br s), 4.98 (1H, br s), 3.83 (2H, m) 3.71 (1H, m), 3.52 (1H, br s), 2.42 (3H, s), 2.16 (1H, m), 1.80 (1H, br s). M+1 = 303

SCHEME 9



Synthesis of tert-butyl-1-[2-(isopropylamino)-2-oxoethyl]piperidin-4-ylcarbamate

tert-Butyl piperidin-4-ylcarbamate (100.0 mg, 0.499 mmol) along with N,N-diisopropylethylamine (64.5 mg, 0.50 mmol), and methylene chloride (3.0 mL) were added to a reaction flask. 1-Bromo-N-isopropylacetamide (89.8 mg, 0.50 mmol) was slowly added to the flask and the reaction allowed to stir for an hour. The solvents were removed under high vac and the tert-butyl-1-[3-(isopropylamino)-2-oxopropyl]piperidin-4-ylcarbamate used as is in the next step.

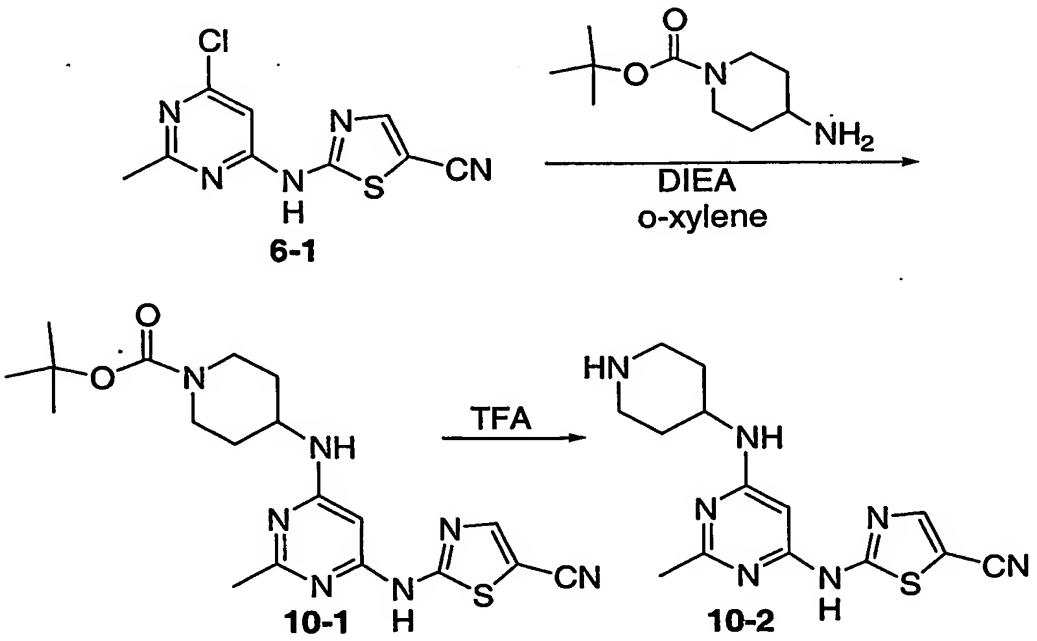
Synthesis of 2-(4-aminopiperidin-1-yl)-N-isopropylacetamide

The tert-butyl 1-[2-(isopropylamino)-2-oxoethyl]piperidin-4-ylcarbamate was treated neat with trifluoroacetic acid and warmed at 60°C for approximately 15 minutes. The reaction was then cooled to room temperature and all of the excess TFA removed under high vacuum. The 1-(4-aminopiperidin1-yl)-3-(isopropylamino)acetone obtained was used as is in the next step.

Synthesis of 2-[-({6-[(5-cyano-1,3-triazol-2-ylamino]-2-methylpyrimidin-4-yl} amino)piperidin-1-yl]-N-isopropylacetamide (9-1)

2-(4-Aminopiperidin-1-yl)-N-isopropylacetamide (95.0 mg, 0.50mmol) was treated with excess N,N-diisopropylethylamine (308 mg, 2.38 mmol) along with 2-[(6-chloro-2-methylpyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile (**6-1**) (100.0 mg, 0.397 mmol) and n-butanol (2.0 mL). The reaction was heated at 100°C for three days. The solvent was removed and the crude material purified on the prep HPLC. This yielded 2-[-({6-[(5-cyano-1,3-triazol-2-ylamino]-2-methylpyrimidin-4-yl}amino) piperidin-1-yl]-N-isopropylacetamide as the trifluoroacetic acid salt. ^{1}H-NMR (500 MHz, CD_3OD): 8.02 (1H, s), 6.01 (1H, s), 4.03 (2H, m) 3.90 (2H, br s), 3.70 (2H, br s), 2.56 (3H, s), 2.27 (2H, br s), 1.91 (2H, br s), 1.18(6H, d). M+1 = 415

SCHEME 10



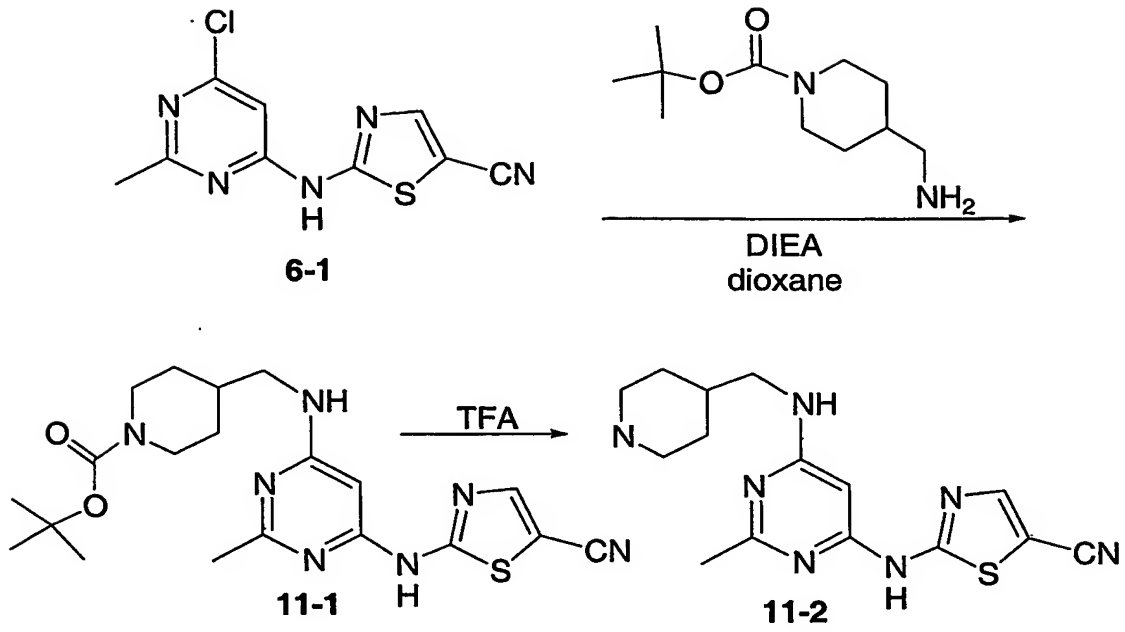
Synthesis of tert-butyl-4-({6-[(5-cyano-1,3-thiazol-2-ylamino]-2-methylpyrimidin-4-yl}amino)piperidine-1-carboxylate (**10-1**)

2-[(6-Chloro-2-methylpyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile (**6-1**) (125.0 mg, 0.50 mmol) was added to a solution of tert-butyl-4-aminopiperdine-1-carboxylate (201 mg, 1.0 mmol) and N,N-diisopropylethylamine (0.27 mL, 1.5 mmol) in o-xylene (3.0 mL). The reaction mixture was heated at reflux for three days. The reaction was cooled and excess solvents removed. The residue was purified by chromatography on silica gel eluting with a 40-80% ethyl acetate/hexane gradient The appropriate fractions were combined and the solvents evaporated to give the desired product as a crystalline freebase, mp: >250°C. ^{1}H-NMR (500 MHz, $CDCl_3$): 9.15 (1H, br s), 7.91 (1H, s), 5.56 (1H, s), 4.88 (1H, br s) 4.06 (2H, br s), 3.72 (1H, m), 2.99 (2H, t J=10.5 Hz), 2.52 (3H, s),2.01 (2H, br d, J=12.5Hz), 1.48 (9H, s), 1.42 (2H, m). M+1 = 416.3

Synthesis of 2-{[2-methyl-6-(piperidin-4-ylamino)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile (**10-2**)

A solution of tert-butyl-4-({6-[(5-cyano-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}amino)piperidine-1-carboxylate (60 mg, 0.144 mmol) in chloroform (5 mL) containing TFA (1.0 mL) was stirred at room temperature over night. The solvents were evaporated and the residue was chased with chloroform (2X). The residue was dissolved in a minimum amount of methanol and diluted with diethyl ether and the title compound crystallized out as the TFA salt, mp: >250°C. ^{1}H-NMR (500 MHz, DMSO-d_6): 12.0 (1H, s), 8.52(1H, br s), 8.32(1H, br s), 8.24 (1H,s), 7.47 (1H, br d, J=6.3Hz), 5.93(1H,s), 3.28(2H, br d J=11.6Hz), 3.05 (2H,m), 2.41(3H, s), 2.02(2H,br d, J=13.5Hz), 1.60 (2H,m). M+1 = 316.3

SCHEME 11



Synthesis of tert-butyl-4-({6-[(5-cyano-1,3-thiazol-2-yl)amino]methyl}-2-methylpyrimidin-4-yl}amino)piperidine-1-carboxylate (11-1)

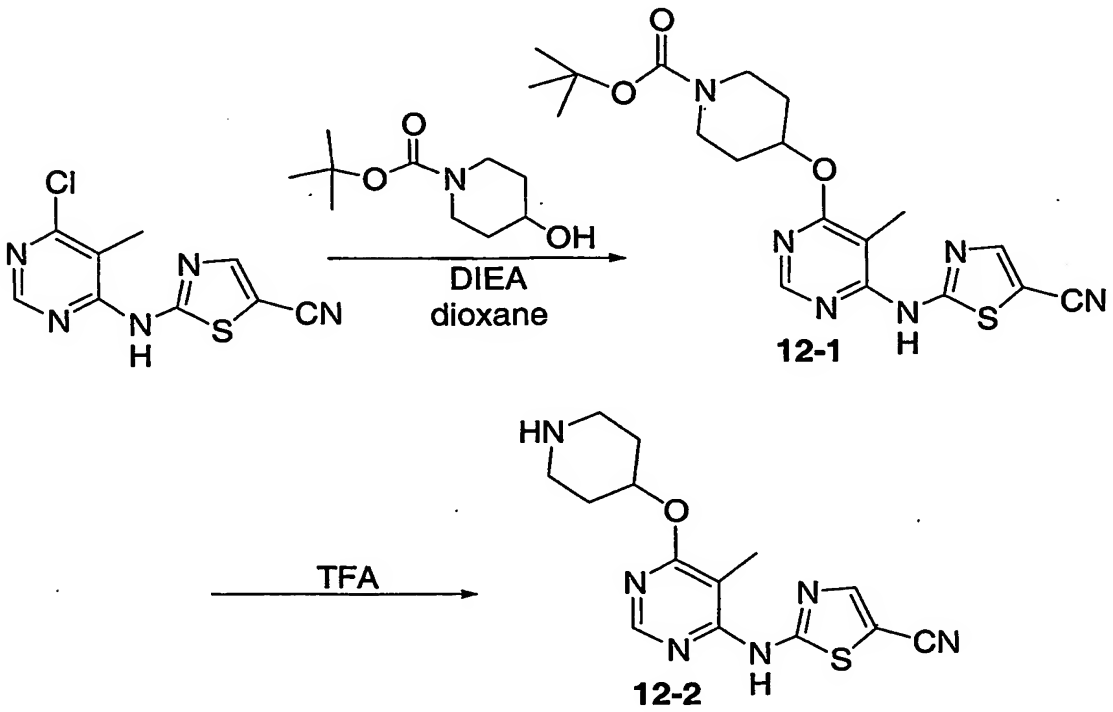
2-[(6-Chloro-2-methylpyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile (**6-1**) (125.0 mg, 0.50 mmol) was added to a solution of tert-butyl-4-aminomethylpiperdine-1-carboxylate (142 mg, 0.66 mmol) and N,N-diisopropyl-ethylamine (0.25 mL, 1.44 mmol) in dioxane (1.5 mL). The reaction mixture was heated at reflux for three days. The reaction was cooled and ethyl acetate (4 mL) was added. Product slowly precipitated and was collected by filtration. The mother liquors were purified further by chromatography on silica gel eluting with ethyl acetate. The appropriate fractions were combined and the solvents evaporated to give the desired product as a crystalline freebase, mp: >250°C. ^{1}H-NMR (500 MHz, $CDCl_3$):11.15 (1H, s), 7.89 (1H, s), 5.76 (1H, s),5.27 (1H, br s), 4.12 (2H, br s), 3.16 (2H, br s), 2.69 (2H, m), 2.48 (3H, s), 1.73(2H, br d, J=9.5Hz), 1.45 (9H, s), 1.21 (2H, m). M+1 = 430.4

Synthesis of 2-({2-methyl-6-[(piperidin-4-ylmethyl)amino]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile (11-2)

A solution of tert-butyl-4-({6-[(5-cyano-1,3-thiazol-2-yl)amino] methyl}-2-methylpyrimidin-4-yl}amino)piperidine-1-carboxylate (112 mg, 0.26 mmol) in chloroform (5 mL) containing TFA (1.0 mL) was stirred at room temperature over night. The solvents were evaporated and the residue was dissolved in a minimum amount of methanol and diluted with

diethyl ether and the title compound crystallized out as the TFA salt, mp: >250°C. ^{1}H-NMR (500 MHz, DMSO-d6):11.9(1H, s), 8.58 (1H, br s), 8.23(1H,s), 7.89(1H, br s),7.52(1H, br s), 5.92 (1H,br s), 3.27(2H, br d J=10.7Hz), 2.86 (2H,br q), 2.36(3H, s), 1.81(2H,br d, J=13.4Hz), 1.31 (2H,br q). M+1 = 330.3

SCHEME 12



Synthesis of tert-butyl-4-({6-[(5-cyano-1,3-triazol-2-ylamino]-5-methylpyrimidin-4-yl}oxy)piperidine-1-carboxylate (12-1)

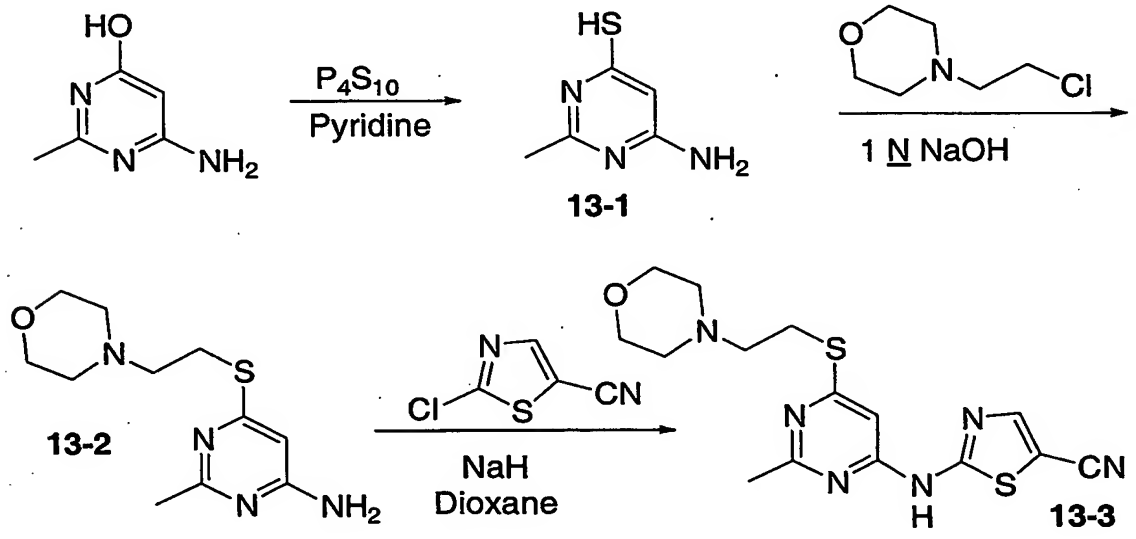
Sodium hydride (60% in mineral oil, 80mg 2.0 mmol) was added to a solution of tert-butyl-4-hydroxypiperdine-1-carboxylate (151 mg, 0.75 mmol) in toluene (2.0 mL). After gas evolution ceased 2-[(6-chloro-5-methylpyrimidin-4-yl) amino]-1,3-thiazole-5-carbonitrile (126.0 mg, 0.50 mmol) was added to the reaction. Anhydrous dioxane (1 mL) and dry DMSO (0.5 mL) were added to dissolve the resultant suspension and the reaction mixture was heated at reflux for six hours. The reaction was cooled and ethyl acetate was added. The organic layer was washed with $NaHCO_3$, dried, filtered, and the solvents evaporated. The residue was purified by chromatography on silica gel eluting with a 40% ethyl acetate/hexane. The appropriate fractions were combined and the solvents evaporated to give the desired product as a white solid. ^{1}H-

NMR (500 MHz, $CDCl_3$): 8.48(1H, s), 8.46 (1H, br s), 7.94 (1H, s), 5.36 (1H, m), 3.74 (2H, m), 3.36 (2H, m), 2.15 (3H, s), 2.00 (2H, m), 1.77 (2H, m), 1.48 (9H, s). M+1 = 417.3

Synthesis of 2-{[5-methyl-6-(piperidin-4-ylamino)pyrimidin-4-yl]oxy}-1,3-thiazole-5-carbonitrile (12-2)

A solution of tert-butyl-4-({6-[(5-cyano-1,3-thiazol-2-yl)amino]-5-methylpyrimidin-4-yl}oxy)piperidine-1-carboxylate (64 mg, 0.15 mmol) in chloro-form (6 mL) containing TFA (2.0 mL) was stirred at room temperature over night. The solvents were evaporated and the residue was chased with chloroform (2X). The residue was dissolved in a minimum amount of methanol and diluted with diethyl ether and the title compound crystallized as the TFA salt, mp: 214-216°C. ^{1}H-NMR (500 MHz, DMSO-d_6):11.8 (1H, br s), 8.56(1H, s), 8.52(1H,br s), 8.36 (1H, s), 5.36(1H,m), 3.25(2H, m), 3.18 (2H,m), 2.19(3H, s), 2.12 (2H,m), 1.91 (2H,m). M+1 = 317.3

SCHEME 13



Synthesis of 6-amino-2-methylpyrimidine-4-thiol (13-1)

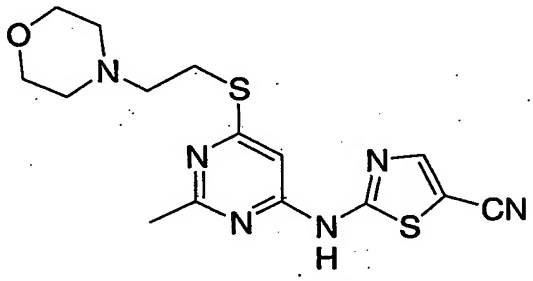
The title compound was prepared by modification of the procedure described Chem. Pharm. Bull (Tokyo), 11, 912-917 (1963) [Chem. Abstr. 60:1748a]. Phosphorus pentasulfide (12.2 gm, 50 mmol) was added to pyridine (80 mL) and stirred for 30 minutes. Then 6-chloro-2-methylpyrimidin-4-amine (2.5 gm, 20 mmol) was added and the mixture was heated at 110°C for 24 hours. The pyridine was removed under reduced pressure and the yellow solid suspended in water (50 mL). 5 N NaOH was added until nearly all solid dissolved in the

solution. This solution was filtered and acetic acid was added as the yellow product precipitated. After cooling this mixture in an ice bath the product was collected by filtration, rinsed with water and air-dried to give 6-amino-2-methylpyrimidine-4-thiol. ^{1}H-NMR (500 MHz, DMSO-d$_6$): 12.2 (1H, s), 7.02 (2H, br s), 6.00(1H, s), 2.23(3H, s).

Synthesis of 2-methyl-6-[(2-morpholin-4-ylethyl)thio]pyrimidin-4-amine (13-2)

Dissolved 6-amino-2-methylpyrimidine-4-thiol (102 mg, 0.72 mmol) in 1 N NaOH (2.5 mL) and added N-(2-chloroethyl)morpholine hydrochloride (140 mg, 0.75 mmol) to the solution. After stirring at ambient temperature for 18 hours the pH was adjusted to ~4 by addition of acetic acid and the product was isolated by extraction into ethyl acetate. This organic layer was dried over anhydrous sodium sulfate, the solution filtered, and the solvent removed. The residue was triturated with diethyl ether to the title compound as a yellow solid. ^{1}H-NMR (500 MHz, CDCl$_3$): 6.14 (1H, s), 4.67 (2H, br s), 3.74 (4H,t, J=4.6 Hz), 3.27 (2H,t, J=7.5 Hz), 2.67 (2H, t, J=7.6Hz), 2.54 (4H, m), 2.45 (3H, s). M+1 = 255.4

Synthesis of 2-({2-methyl-6-[(2-morpholin-4-ylethyl)thio]pyrimidin-4-yl}amino)-1,3-thiazole-5-carbonitrile (13-3)

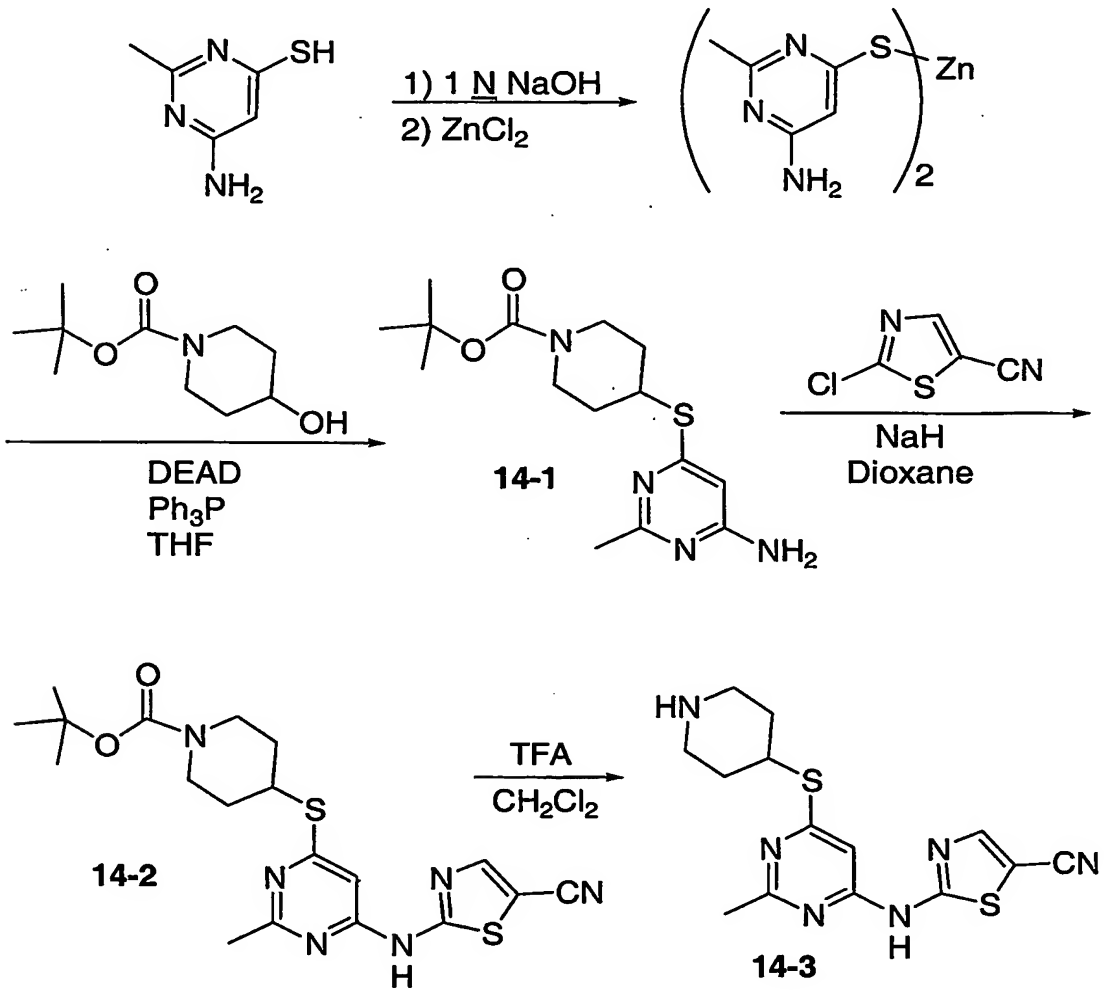


13-3

Sodium hydride (60% in mineral oil, 65 mg, 1.6 mmol) was added to a partial suspension of 2-methyl-6-[(2-morpholin-4-ylethyl)thio]pyrimidin-4-amine (100 mg, 0.39 mmol) and stirred for 15 minutes. 2-Chloro-1,3-thiazole-5-carbonitrile (58 mg, 0.40 mmol) was then added and the mixture was heated at 60°C and the progress of the reaction was monitored by LC/MS. Additional sodium hydride (43 mg) and 2-chloro-1,3-thiazole-5-carbonitrile (47 mg) was added to drive reaction to near completion. The reaction mixture was cooled, diluted with ethyl acetate, acidified with some acetic acid and then washed with aq. satd. sodium bicarbonate. The dried organic solution was filtered and the solvent removed. The residue was subjected to column chromatography on silica gel and eluted with a 1-3% methanol/ ethyl acetate (saturated NH$_4$OH) gradient. The appropriate fractions were combined and the solvent evaporated. The

residue was triturated with diethyl ether/ethyl acetate to give the title compound as a freebase, mp: 197-198°C. ^{1}H-NMR (500 MHz, DMSO-d6): 12.2(1H,br s), 8.33 (1H,s), 6.76 (1H, s), 3.57 (4H,m), 3.28 (2H, br t, J=7.2 Hz), 2.61 (2H, m), 2.57 (3H, s), 1.98 (2H,m), 2.46 (4H,m). M=1 = 363.3

SCHEME 14



Synthesis of tert-butyl 4-[(6-amino-2-methylpyrimidin-4-yl)thio]piperidine-1-carboxylate (14-1)

Potassium hydroxide (86%, 260 mg, 4 mmol) was dissolved in a mixture of ethanol (15 mL) and methanol (5 mL) and then 6-amino-2-methylpyrimidine-4-thiol (564 mg, 4 mmol) was added. This mixture was stirred and slightly warmed until most of solid had dissolved. A solution of 1 M zinc chloride in ether (2 mL) was added dropwise as a precipitate formed instantly. After stirring for one half hour, the solid was isolated by filtration and rinsed

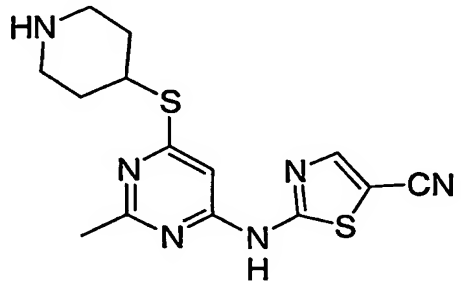
with ethanol, methanol and diethyl ether and air-dried to give bis-(6-amino-2-methylpyrimidine-4-thio) zinc.

Tert-butyl 4-hydroxypiperdine-1-carboxylate (285 mg, 1.4 mmol) was dissolved in dry tetra-hydrofuran (5 mL) and then bis-(6-amino-2-methylpyrimidine-4-thio) zinc (350 mg, 1 mmol) and triphenyl phosphine (739 mg, 2.8 mmol) were added. This mixture was kept in the dark (covered with aluminum foil) and cooled in an ice bath and diethyl diazodicarboxylate (DEAD) (0.44 mL, ~2.8 mmol) was added dropwise via syringe. The reaction was stirred for ~18 hours. The solvent was removed under vacuum and the residue was subjected to chromatography on silica gel eluting with a 20-80% ethyl acetate/hexane gradient. Fractions containing product and triphenyl phosphine oxide were combined and the solvent removed. This mixture was rechromatographed on silica gel and eluted with 0-3% methanol/ethyl acetate. The appropriate fractions were combined and the solvent removed to give the title compound as a viscous semisolid. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.12 (1H, s), 3.99 (H, m), 3.92 (2H, br s), 3.09 (2H,t, J=11 Hz), 2.45 (3H, s), 2.04 (2H, br d, J=13 Hz), 1.62 (2H, m), 1.46 (9H, s). M+1 = 325.4

Synthesis of tert-butyl 4-({6-[(5-cyano-1,3-thiazol-2-yl)amino]pyrimidin-4-yl}thio) piperidine-1-carboxylate (14-2)

Sodium hydride (60% in mineral oil, 22 mg, ~0.5 mmol) was added to a solution of tert-butyl 4-[(6-aminopyrimidin-4-yl)thio]piperidine-1-carboxylate (37 mg, 0.114 mmol) in dry dioxane (2 mL). After gas evolution ceased (~1/4 hour) 2-chloro-1,3-thiazole-5-carbonitrile (19 mg, 0.13 mmol) was added and the reaction was warmed to ~60°C for 22 hours. By LC/MS the reaction was incomplete so additional sodium hydride (19 mg, 0.5 mmol) and 2-chloro-1,3-thiazole-5-carbonitrile (19 mg, 0.13 mmol) were added and the reaction mixture was heated for another 20 hours. The cooled reaction was diluted with ethyl acetate and acetic acid (0.09 mL, 1.5 mmol) was added. This solution was washed with $NaHCO_3$ solution. The ethyl acetate extract was dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was chromatographed on silica gel eluting with a 30-80% ethyl acetate/hexane gradient. The appropriate fractions were combined and the solvents removed to give the title compound as a white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 10.5 (1H, br s), 7.96 (1H,s), 6.49 (1H, s), 4.14 (1H,m), 3.94 (2H, br s), 3.13(2H, m), 2.67 (3H, s), 2.07 (2H,br d, J=7.8 Hz), 1.66 (2H,m), 1.48 (9H, s). M+1 = 433.4

Synthesis of 2-{[6-(piperidin-4-ylthio)pyrimidin-4-yl]amino}-1,3-thiazole-5-carbonitrile (14-3)



14-3

A solution of tert-butyl 4-({6-[(5-cyano-1,3-thiazol-2-yl)amino] pyrimidin-4-yl}thio)piperidine-1-carboxylate (10 mg, 0.023 mmol) in methylene chloride (4 mL) containing TFA (0.5 mL) was stirred at room temperature over night. The solvents were evaporated and the residue was chased with chloroform (2X). This residue was triturated with diethyl ether to give the title compound as a TFA salt, mp: 243-244°C. ^{1}H-NMR (500 MHz, DMSO-d$_6$): 12.2 (1H, br s), 8.58(1H, br s), 8.38 (1H, br s), 8.35 (1H,s), 6.77 (1H,s), 4.06 (1H,m), 3.29(2H,m), 3.11 (2H,m), 2.60 (3H, s), 2.11 (2H,br d, J=14 Hz), 1.78 (2H,br q, J=10.6 Hz). M+1 = 333.3